The New England
Journal of Medicine

Copyright, 1947, by the Massachusetts Medical Society

Volume 236 APRIL 10, 1947 Number 15

THE USE OF CURARE IN ANESTHESIA*

EDWARD C. ALLEN, M.D.,† AND URBAN H. EVERSOLE, M.D.‡

BOSTON

FOR the past few centuries, curare has been dismissed lightly as being synonymous with the generic name of several arrow poisons of certain South American Indians, but investigation of its pharmacologic action and clinical application in the past decade has shown this drug to hold great promise to the anesthesiologist. The first descriptions of this so-called "arrow poison" were brought back to the civilized world by Sir Walter Raleigh in 1595 following his journey to Guiana and up the Orinoco.[1] Because of the variable source and potency of the drug and because of the toxic effects due to the impurities in the crude preparations, little advance was made in its investigation until the researches of the eminent physiologist Claude Bernard on its use in hydrophobia, chorea, tetanus and epilepsy. From his work came the first realization that the physiologic action of curare takes place at the myoneural junction.

Full credit for the modern development of curare must be given to Gill,[1] who spent much time in the Amazonian jungles and in 1938 brought back to this country adequate supplies of the drug for investigative work. From that time on there has been no standstill in research on the properties of this drug. Gill[2] recently cleared up what he considered misconceptions about the source and development of the drug. He stated that curare is not derived from a single species of plants but is a mixture of botanical components, widely distributed throughout northern and western South America, more particularly in regions of Amazonian drainage. The type of primitive container, whether it is a bamboo tube or gourd, bears no relation to the type of curare it contains.

McIntyre[3] and Bennett,[4, 5] at the University of Nebraska, conducted the first modern pharmacologic study and clinical trial of the drug. It was first used in the field of psychiatry in an attempt to overcome some of the less desirable accompaniments of convulsive shock therapy. To Griffith and Johnson,[6] of Montreal, goes the credit for the introduction of curare to the field of anesthesiology in 1942. They reported the effectiveness of this drug in producing muscular relaxation in patients anesthetized with cyclopropane. Numerous reports of the successful use of curare to enhance muscular relaxation in conjunction with all types of general anesthetics were subsequently made.[7–15]

Intocostrin§ — a standardized product of greater purity — has been available since 1940. It is a clear, amber-colored solution supplied in rubber-stoppered vials containing 20 mg. of the crude drug per cubic centimeter. It is biologically assayed and tested in man before being distributed. It is sufficiently free of hydrolyzable resins so that it is not subject to clouding for at least a year if kept refrigerated. Little has been mentioned in the literature concerning its chemical nature, although it has been said to resemble bisbenzylisoquinoline alkaloid.[16] It is best administered intravenously but can be given intramuscularly, allowance for the time interval for effective action being made. Intocostrin is nonirritating to tissues even when given subcutaneously.

The primary site of physiologic action of curare is peripherally at the myoneural junction. The exact nature of this mechanism is not completely understood. The muscle response to the acetylcholine influence at the myoneural junction is markedly diminished either by an increase in the threshold of reaction to the normal concentration of acetylcholine or by a sort of neutralization of the acetylcholine activity. Regardless of the mechanism, the result of administration is a paresis or paralysis of the voluntary musculature throughout the body. There is a progressive action on muscle groups starting with the head and neck and extending downward to the trunk and extremities and lastly to the muscles of respiration. Fortunately, the diaphragm is the last muscle to be affected. There seems to be a paresis first in the short muscles of the head supplied by cranial nerves and then the longer muscles of the neck, trunk and extremities.

*From the Department of Anesthesiology, Lahey Clinic.
†Anesthesiologist, Lahey Clinic.
‡Anesthesiologist, Lahey Clinic; anesthesiologist, New England Baptist and New England Deaconess hospitals.

§Obtainable from E. R. Squibb and Sons, New York City.

Recovery from the paralysis of curare appears to be in the reverse order. With increased doses, the paresis of respiratory muscles may go on to complete paralysis. This is the one great danger in its use, particularly if facilities are not readily available to overcome it with effective artificial respiration. If curare is given to a conscious patient the results may be distressing to both the physician and the patient. The patient first notices diplopia or haziness of vision and weakness of the eyelids and then starts to salivate, only to find that he is unable to move his jaws, swallow or cough. This is followed by inability to raise the head, inability to move the extremities and, finally, difficulty in breathing. These symptoms are so distressing as sometimes to produce in the patient a fear of impending death. The administration of large enough doses of curare to conscious patients to cause these symptoms is unwarranted. The drug is supposed to have no central action, but further experimental work may disprove this assumption. Whitacre and Fisher[17] have shown that patients can be made unconscious by exceptionally large doses of curare. Smith[18] permitted the drug to be administered to him until complete respiratory paralysis had occurred and stated that he had not lost consciousness. Fegler[19] demonstrated that curare affected the respiratory center in animals before the full development of its peripheral action. Stimuli that ordinarily increase or decrease the frequency and amplitude of respiration had no effect during the period of respiratory inhibition. For many years, crude curare was found to be extremely toxic to the cardiovascular system, but this has now been proved to have been the result of impurities in the preparation. There are no electrocardiographic changes in either normal or diseased hearts during curare administration, but it must be remembered that the respiratory depressing effect may be responsible for the production of apnea and hypoxia, which in turn may aggravate cardiac damage.[20] The hypotension seen after curare is transient. The pulse is unaffected, and the drop in the blood pressure is only about 20 mm. of mercury and usually lasts for only a few minutes. It is questionable whether this is the result of a block in transmission between preganglionic and postganglionic fibers in the sympathetic system or of poor peripheral venous return resulting from the loss of muscle tone. Curare seems to produce a temporary loss of tone and peristaltic activity of the small bowel.[21]

A safety factor in the administration of curare is the rapidity with which it is eliminated from the body. Most of it is broken down in the liver, and the remainder is excreted unchanged by the kidneys.[22]

Laboratory and clinical experiences have yet to prove certain actions of curare, such as its effect on involuntary muscles, placental permeability, blood and blood-forming tissue and also its effect on cells of the central nervous system. It is thought that its action does not extend to structures innervated by postganglionic fibers, such as the glands and smooth muscle. At any rate, no permanent pathologic change has yet been demonstrated following its use.

Curare, a nonanesthetic and nonhypnotic drug, was introduced into the field of anesthesiology because of the excellent muscular relaxation that it provided. Far too frequently, the situation has arisen in the course of an operation when the surgeon's work is hampered because of the poor relaxation of the patient. The anesthetist in despair may deepen the anesthesia to a point that is physiologically unsound and definitely detrimental to the patient. This situation need no longer exist now that curare is available. This statement is not to be construed to mean that the drug is advised as an outlet or excuse for a poorly planned or poorly administered anesthetic. On the contrary, curare is advocated by Griffith and Johnson[6] and by Cullen[23] in a planned technic of administration in combination with cyclopropane. This means that the anesthesia can be carried in a relatively light plane and still provide adequate relaxation. The technic consists of putting the patient to sleep in the usual manner with cyclopropane and giving the first dose of curare just as the skin incision is made. Griffith[6] originally used 100 mg. (units) practically routinely as the first dose, whereas Cullen[23] advised an average initial dose of 60 mg. in patients from twenty to seventy years of age. After an interval of three to five minutes, if the initial dose is found to be inadequate, an additional dose of 40 mg. is administered, and if this is also inadequate a third injection, one of 20 mg., is given. The initial dose may be sufficient if the operation does not last longer than forty-five minutes. If the procedure is longer, supplementary doses should be given, a half to a third the initial dose being used. The drug has been given to both young and old patients and to those who are both good and poor risks. In small infants dosages of from 4 to 6 mg. have been employed. Experience has shown that an intravenous injection is usually effective in thirty to sixty seconds and lasts about twenty minutes. The total dosage given during an operation is not too important. There will be a return of adequate respiratory excursions long before the return of muscle tonus. The one factor that must be observed closely is the effect of each dose on the respiration.

As stated above, the anesthetist must definitely be prepared to treat respiratory depression or apnea. Poor respiratory exchange must not be tolerated for any length of time because of the likelihood that a hypoxic state and the accumulation of carbon dioxide will develop. Adequate airways must be available, and in fairness to the patient, the anesthetist should have some knowledge of the technic of endotracheal intubation. This, indeed, is manda-

tory in some cases in which actual laryngeal spasm occurs as a result of inadequate general anesthesia used coincidentally with the injection of curare. Knight,[24] on the other hand, has found curare to be practically specific in cases in which laryngeal spasm develops during anesthesia. This point is still quite controversial.

In patients in whom shock is present or appears imminent, and in elderly or debilitated patients, it is wise to use smaller doses than are ordinarily employed.

Cyclopropane appears to be the ideal anesthetic agent to be used in combination with curare. The patient is carried in a light plane (usually the second) of anesthesia throughout. Curare neither increases nor decreases the irritability of the heart when employed with cyclopropane. This combination affords a pleasant and rapid induction and recovery with no aftereffects, and its most ardent supporters believe that the relaxation compares favorably with that obtained with spinal anesthesia.

Curare has been used with both the weaker gases nitrous oxide and ethylene.[9, 25] Neither of these alone is capable of causing good flaccid muscular relaxation, and yet the relaxation from its combination with curare is satisfactory for upper abdominal operations. Much larger doses of curare are employed with these gases than with the more potent anesthetic agents, and in some cases there has been marked respiratory depression.

When curare is used to supplement ether anesthesia, great precaution must be taken in its administration. Ether has been demonstrated to have an action similar to that of curare, so that the myoneural junction is already partially paralyzed. There is a sort of cumulative action so that all the effects of curare will be increased, especially the length of respiratory depression. Thus, it is advisable to use smaller doses of curare, either 20 or 40 mg., instead of the usual 60 mg. Several cases of severe circulatory depression after the combination of ether and curare have been reported. Cullen[26] stated that this curariform action is an attribute not only of ether but also of tribromethanol and Pentothal Sodium, especially when the blood concentration is high.

The recent literature contains favorable reports on the combined use of curare and Pentothal,[27] but again a word of warning is necessary. It must be remembered that with this combination two respiratory depressants are being used at the same time. Provided that the anesthetist is fully capable of dealing with any respiratory problem that may arise, — whether it is depression or obstruction, — there is no great danger in the combination. Pentothal and curare should not be given through the same needle because of the formation of a precipitate. Recent development of a crystalline product is reported to overcome this disadvantage. Experience has shown that the total dose of Pentothal is definitely reduced when the drug is used in conjunction with curare and also that the period of postoperative narcosis is considerably shortened.

There are a few definite contraindications to the use of curare. It should not be administered when myasthenia gravis is present or when there exists the least possibility that the anesthetist will be unable to deal with the problem of artificial respiration. It probably should not be used in patients with suspected liver or renal impairment.

Although prostigmine is the direct antidote for curare, there have been no reports of its use even in cases in which large doses of curare were given and periods of apnea resulted. Treatment has consisted solely of artificial respiration.

Curare has proved to be a valuable adjunct to spinal anesthesia. This is true when a single-dose agent has produced anesthesia of insufficient duration for the completion of the operation. The total amount of spinal-anesthetic agent needed when the continuous technic is employed is often materially lessened by the administration of curare toward the end of the operation. This may be significant in view of the fact that there is considerable evidence that neurologic complications after a spinal anesthetic may bear a relation to the total amount of drug used.

Curare has been used to advantage in several abdominal operations for massive hemorrhage from gastric or duodenal ulcer in which the patient was bleeding profusely and was in a state of severe shock on arrival in the operating room. Since spinal anesthesia was contraindicated because of the marked hypotension, these patients were carried on cyclopropane and curare, a technic similar to that advocated by Cullen being used. The cyclopropane provided anesthesia with a sufficiently high oxygen concentration to prevent the development of hypoxia, and the curare provided adequate relaxation — almost equivalent to that of spinal anesthesia.

The use of curare in combination with Pentothal is becoming more extensive. Bronchoscopies and esophagoscopies are easily performed with this combination. The technic should include a thorough cocainization of the pharynx and larynx before the administration of either drug. Curare is usually given while the patient is awake, the dosage depending on the age, size and vigor of the patient. The average dose is 60 mg. The effectiveness of the curare is determined by the patient's ability to raise his head or arms from the table. When this ability is impaired, the Pentothal is administered in the usual manner. When there is no impairment in ability to raise the head, it is evident that the dosage of curare is inadequate, and a second dose is administered. This technic has obviated the necessity of deep ether anesthesia for difficult endoscopies and has appreciably shortened the time for these procedures.

For more extensive operations, the combination of curare, Pentothal and nitrous oxide has been used; these include laminectomies, splanchnicectomies and more recently, intrathoracic operations. Since this combination eliminates the employment of inflammable agents, it permits the use of high-frequency electrosurgical apparatus in the chest. Induction is carried out in the same manner as in endoscopy. Subsequent doses of curare are given at intervals of twenty to thirty minutes, according to the need for relaxation at the time. It has been our observation that the total amount of Pentothal in these cases has been decreased. Needless to say, the patient's respirations must not be so depressed that he suffers from even transient hypoxia.

* * *

In the course of a few years, curare has proved itself to be of considerable value in the field of anesthesiology. It is not to be considered a panacea to answer all problems of relaxation, but it is certainly a useful adjunct. Further investigative research will no doubt augment its clinical applicability.

Since this paper was submitted for publication a solution of pure *d*-tubocurarine has become available. This preparation is biologically assayed so that its dosage is the same volume as that for Intocostrin.

605 Commonwealth Avenue

References

1. Gill, R. C. *White Water and Black Magic.* 369 pp. New York: Henry Holt & Company, Inc., 1940.
2. *Idem.* Curare: misconceptions regarding discovery and development of present form of drug. *Anesthesiology* 7:14-23, 1946.
3. McIntyre, A. R., and King, R. E. d-Tubocurarine chloride and choline esterase. *Science* 97:69, 1943.
4. Bennett, A. E. Preventing traumatic complications in convulsive shock therapy by curare. *J. A. M. A.* 114:322-324, 1940.
5. *Idem.* Curare: preventive of traumatic complications in convulsive shock therapy. (Including preliminary report on synthetic curare-like drug.) *Am. J. Psychiat.* 97:1040-1060, 1941.
6. Griffith, H. R., and Johnson, G. E. Use of curare in general anesthesia. *Anesthesiology* 3:418-420, 1942.
7. Smith, S. M. Curare as adjuvant during inhalation anesthesia: report of fifty cases. *Rocky Mountain M. J.* 41:313-317, 1944.
8. Knight, R. T., and Baird, J. W. Anesthesia for aging and aged. *Journal-Lancet* 64:183-185, 1944.
9. Waters, R. M. Nitrous oxide-oxygen and curare. *Anesthesiology* 5: 618, 1944.
10. Cullen, S. C. Use of curare in anesthesia. *South. M. J.* 38:144-148, 1945.
11. Griffith, H. R. Curare as aid to anaesthetist. *Lancet* 2:74, 1945.
12. *Idem.* Use of curare in anaesthesia and for other clinical purposes. *Canad. M. A. J.* 50:144-147, 1944.
13. Cole, F. Use of curare in anesthesia: review of 100 cases. *Anesthesiology* 6:48-56, 1945.
14. Cullen, S. C. Clinical and laboratory observations on use of curare during inhalation anesthesia. *Anesthesiology* 5:166-173, 1944.
15. Eversole, U. H. Use of curare in anesthesia. *S. Clin. North America* 26:709-714, 1946.
16. Wintersteiner, O., and Dutcher, J. D. Curare alkaloids from Chondodendron tomentosum. *Science* 97:467-470, 1943.
17. Whitacre, R. J., and Fisher, A. J. Clinical observations on use of curare in anesthesia. *Anesthesiology* 6:124-130, 1945.
18. Smith, S. Personal communication.
19. Fegler, J. Action of curare on respiratory centre. *J. Physiol.* 100: 417-422, 1942.
20. Ruskin, A., Ewalt, J., and Decherd, G. M., Jr. Electrocardiogram of curarized human patients. *Dis. Nerv. System* 4:335-341, 1943.
21. Gross, E. G., and Cullen, S. C. Action of curare on smooth muscle of small intestine and on blood pressure. *Anesthesiology* 6:231-238, 1945.
22. Griffith, H. R. Curare in anesthesia. *J. A. M. A.* 127:642-644, 1945.
23. Cullen, S. C. Use of curare for improvement of abdominal muscle relaxation during inhalation anesthesia: report on 131 cases. *Surgery* 14:261-266, 1943.
24. Knight, R. T. Use of curare in anesthesia. *Minnesota Med.* 27: 667-670, 1944.
25. Harroun, P., Beckert, F. E., and Hathaway, H. R. Curare and nitrous oxide anesthesia for lengthy operations. *Anesthesiology* 7: 24-28, 1946.
26. Gross, E. G., and Cullen, S. C. Effects of anesthetic agents on muscular contraction. *J. Pharmacol. & Exper. Therap.* 78:358-365, 1943.
27. Brody, J. Use of curare in sodium pentothal-nitrous oxide-oxygen anesthesia. *Anesthesiology* 6:381-384, 1945.

EXPERIENCES WITH CURARE IN ANESTHESIA*

SIDNEY C. WIGGIN, M.D.,† PHILIP E. SCHULTZ, M.D.,‡ AND PETER SAUNDERS, M.D.§

BOSTON

THE use of curare in anesthesia has rapidly gained popularity within the past few years. Numerous papers, which agree on its usefulness, have been published since the initial study of Griffith.[1] These papers describe different methods of administration, advantages, limitations and possible disadvantages of the drug.[2–9] There have also been publications of experimental studies that give further information.[10–14]

The main purposes of this paper are to consider the indications for curare and its comparison with other agents and to present experience with the use of curare (Intocostrin¶) in 450 cases. The basis of discussion of the results in these cases lies in the segregation into four distinct groups in which the special qualifications and the adaptation of curare are described. It will be noted that other uses of curare — for example, in bronchoscopy and cesarean section — are not considered.

The first group in which curare was administered comprised cases of elective abdominal surgery in which the choice of anesthesia presented no particular problem, for these cases were adaptable for any conventional type of anesthesia. With this group as a standard it was possible to evaluate the technic.

The method of administering curare with a light general anesthetic was that described by Cullen.[2] The agents used with curare were cyclopropane, Pentothal Sodium, nitrous oxide, ether and various combinations. The experiences and results corresponded with those of Cullen. Relaxation was found to be extremely satisfactory; in most cases, it was similar to the complete relaxation attained in spinal anesthesia. In quite a few cases, however, the onset of relaxation was delayed, additional doses and time being required. On the basis of this

*From the Department of Anesthesiology, Boston City Hospital.

†Professor of anesthesiology, Tufts College Medical School; director of anesthesia, Boston City Hospital and Faulkner Hospital.

‡Instructor in anesthesiology, Boston University School of Medicine; visiting anesthetist, Boston City Hospital.

§Assistant in anesthesiology, Tufts College Medical School and Boston University School of Medicine; junior visiting anesthetist and resident director, Department of Anesthesiology, Boston City Hospital.

¶Kindly supplied by E. R. Squibb and Sons, New York City.

experience, it was found to be more advantageous to begin the administration of curare as much as five to fifteen minutes before the time of expected relaxation. This early onset of administration allowed sufficient time for subsequent doses if required, and permitted another way of administering curare — namely, by repeated small doses. When curare is given in this manner, the anesthesiologist can more closely approximate the proper dose by evaluating the response of the patient to the repeated injections of the drug, rather than depending solely on an arbitrary standard dose administered at the beginning of the operation.

Although efforts were made to use the smallest dose, varying degrees of depressed respiration and respiratory paralysis were experienced in a number of cases. The relatively narrow margin between the optimal dose and that producing respiratory paralysis corresponded to that described by Cullen.[9] It was found that before the respiratory impairment produced by the paralysis of the intercostal muscles and diaphragm, the respirations became depressed in varying degrees. This depression appeared in several cases when the abdominal muscles were not sufficiently relaxed. This phenomenon probably results from the depressant effect of curare directly on the respiratory center. As Fegler[13] demonstrated, the drug influences the respiratory center before the full development of its peripheral action.

During the administration of curare, when the respirations became depressed and the excursions of the breathing bag perceptibly decreased, the respiratory movements were immediately supported by the application of manual compression on the breathing bag, the minute volume exchange being thus increased. In many cases this support to the respiration was followed by periods of apnea with controlled breathing. It would be difficult to determine how often this apnea was primarily due to respiratory paralysis produced by curare or to the so-called "apneic technic." The return of spontaneous respiration occurred on the average in ten or fifteen minutes when the general anesthesia was lightened. Nevertheless, in several cases this return of spontaneous respiration did not occur so readily as in the straight apneic technic. Controlled breathing was probably used more frequently than was absolutely necessary. This procedure seems to be justified by the following supposition: owing to the many factors that have a depressant effect on the respiratory center during anesthesia[15] and to the additional depressing effect of curare, proper oxygenation and carbon dioxide elimination are questionable with the patient's own depressed respiration, whereas they are assured with controlled breathing.

Controlled breathing is therefore a safety measure in cases of depressed respiration in which the sufficiency of the minute volume exchange can be questioned. It is an absolute necessity in cases of respiratory paralysis in which spontaneous respiratory exchange has ceased. Since the need of establishing controlled breathing may arise at any time, curare should be administered only by those whose technical abilities as well as practical and theoretical knowledge of respiratory physiology guarantee uninterrupted and complete oxygenation and carbon dioxide elimination during periods of depressed respiration and apnea. Equally important is the proper functioning of the anesthesia machine and other anesthesia equipment used for controlled breathing.

The principles in this discussion of respiration apply not only to the cases in this group but also to any cases in which curare is used.

The second group included cases in which a single-dose spinal anesthetic for abdominal surgery was used. The surgical procedures in these cases lasted longer than was anticipated, and the effect of the anesthetic wore off at a time when relaxation was still required. Curare was used to provide relaxation.

The following method of administration was found to be the most satisfactory. Whenever there was any indication that the spinal anesthesia had started to wear off — or if there were no such indications but the expected duration of spinal anesthesia had been reached — general anesthesia was induced with either Pentothal or cyclopropane. The patients were maintained for the remainder of the operation in a light plane of the surgical stage of anesthesia. The administration of curare was begun five to fifteen minutes before the closure of the peritoneum, or earlier if the surgeon did not find sufficient relaxation on intra-abdominal manipulation. Curare was given in doses of 20 to 50 mg. every three to five minutes until complete relaxation was obtained. The total amount administered to any one patient ranged between 50 and 160 mg.

Few changes in circulation were noticed following the administration of curare in the cases in this group as well as those in the first group. Only a few patients showed a moderate and transitory decrease in blood pressure. This favorable circulatory response led to the use of the drug in the cases in the following group.

The third group consisted of poor-risk patients requiring abdominal surgery. Many of them suffered from severe, acute blood loss following uncontrollable gastric hemorrhage, ruptured ectopic pregnancy or postoperative internal hemorrhage, and others were in shock owing to advanced abdominal disease, such as perforated peptic ulcer of more than one day's duration, generalized peritonitis or volvulus with gangrenous bowel.

These patients received light premedication. While intravenous fluids and, in most cases, transfusion were being administered, anesthesia was induced and maintained in the first plane of the third stage with cyclopropane. Abundant oxygenation

was provided throughout the operation. The curare was administered in doses of 20 to 50 mg. every three to five minutes, until the surgeon reported satisfactory relaxation. The total dose required in some cases was less than 50 mg., whereas other cases required as much as 120 to 150 mg. during the operating time of two or three hours. The resulting operating conditions were satisfactory.

Light cyclopropane anesthesia with properly administered curare did not seem to burden the handicapped circulation of these patients by adding to the present or impending shock. On the contrary, by the addition of fluid therapy and the tonic action of cyclopropane with high oxygen percentage, the general condition of most of the patients improved during the operation. The clinical course in the cases in which subtotal gastrectomy was performed on patients with uncontrollable gastric hemorrhage was as gratifying as that of a similar case reported by Whitacre.[5] Although several patients in this group were moribund before the operation, there was no death during the operation or during the immediate postoperative period.

The fourth group comprised patients who required endotracheal anesthesia. Curare was given to facilitate the intubation by relaxing the jaw and throat musculature.

The following method of administration was found to be the most satisfactory. Cyclopropane or Pentothal anesthesia was induced, and curare was simultaneously administered in doses of 20 to 50 mg. The first dose was given at the time when anesthesia started, and further doses were given every three or four minutes. Within eight to ten minutes the patient was in the lower first or upper second plane of the third stage, relaxed and breathing quietly with sufficient depth. The intubation, which took place at that time, was easy and smooth in the majority of cases.

There were, however, respiratory disturbances of minor significance following the intubation in a certain number of cases. The regular rhythmic breathing sometimes stopped, and there was complete cessation of breathing, interrupted with occasional jerky inspirations. This respiratory embarrassment lasted in most cases for a few minutes, although there was one case in which it lasted for thirty-five minutes. In some cases, while controlled breathing was being administered during this period of respiratory embarrassment, the inflation of the lungs met with resistance, indicating that the patient was having a bronchial spasm. Whitacre[5] and Griffith[16] call attention to the fact that bronchial spasm occurring during curare administration is due to insufficient depth of the general anesthesia, in addition to the presence of a gross stimulus. The stimulus in these cases was the intubation and the tracheal tube lying in the trachea. In other cases the lungs could be readily inflated, indicating that the apnea was due to respiratory paralysis, which developed during or immediately following the intubation. To avoid such respiratory disturbances, it seems necessary to stay within a narrow margin of proper depth of general anesthesia and of proper dosage and timing of curare.

The administration of curare for intubation in such a manner that the patient is deliberately put into apnea, the intubation taking place during apnea, has the disadvantages that during the intubation the controlled breathing — that is, the oxygenation of the patient — is interrupted and that it is difficult to re-establish spontaneous respiration with sufficient depth of the general anesthesia, both of which may be necessary in intrathoracic operations.

If ether is used as the main anesthetic for the ensuing operation, its administration, in the form of a slow addition to the cyclopropane or Pentothal, may be started before or after intubation. The amount of ether used in such cases need not exceed a third or a fourth of the amount that would be required if curare were not used. An hour and a half to two hours after the intubation is necessary before the ether requirement approximates the usual amount.

The recovery period in cases of all the groups was generally uneventful and brief, corresponding to the findings of others. Three cases, however, presented complications during recovery. Two of these showed postoperative respiratory depression. One patient, who had received cyclopropane and a small amount of ether with curare, recovered four hours after the operation. The other, who had received a spinal anesthetic followed by cyclopropane and curare, had a recovery period lasting seven hours. These patients were in shock, with depressed breathing and with depression of the reflexes during the postoperative interval. They recovered gradually and completely. Neither the surgery performed nor the anesthetic administered seemed to give sufficient reason in either case for this postoperative complication. It appeared reasonable to assume that hypoxia, which probably developed during the period of shallow breathing following the administration of curare, was an important cause. In these cases, which occurred at the beginning of the series, the anesthesiologist did not support the patient's spontaneous shallow breathing. The experiences with these cases in particular led to the conclusion that depressed respiration should be managed as described above.

In the following case postoperative depression was followed by a fatal outcome.

M. M., a 57-year-old woman with bronchial asthma, was operated on for intestinal obstruction of 4 days' duration. Her general condition before operation was fair. The operation included an extensive exploration, a lysis of adhesions and an ileocecostomy. A spinal anesthetic was administered and was supplemented with Pentothal and curare after 1 hour and 25 minutes. Curare was given in repeated doses totaling 100 mg. During the operation, 100 per cent oxygen was administered, and a transfusion was given. The blood

pressure, pulse and respirations showed little change throughout the operation. The patient left the operating table 20 minutes after the last dose of curare had been given. The breathing was approximately normal in depth, at a rate of 28 per minute. There was no obstruction, and the respiratory exchange was good. The patient's color was good. The blood pressure was 120/68, and the pulse 122.

The transportation from the operating room to the ward took about 12 minutes. On arrival in the ward, the patient was extremely cyanotic and did not breathe, although the pulse was satisfactory. Following artificial respiration for 30 minutes, she regained spontaneous breathing but remained comatose. With inhalation and shock therapy and administration of stimulants her condition improved. Six hours after operation, the blood pressure was 98/70, the pulse 124, and the respirations 36. The patient had a corneal reflex, and, on stimulation, moved her head. Two hours later, she went into shock. She expired 12 hours after operation.

It seems probable that the main cause of death in this case was that, in her serious general condition, the patient was subjected to severe hypoxia during the transportation. The asthma may have played a role in further aggravating the failing oxygenation. Unfortunately, the intern accompanying the patient on her way back to the ward did not recognize the respiratory obstruction, which in all probability was the cause of the hypoxia.

* * *

The choice of anesthesia for elective abdominal surgery in good-risk patients up to the introduction of curare was either spinal or deep general anesthesia, with or without the use of an intratracheal tube; other methods, such as intravenous and local anesthesia and varying combinations, were rarely employed. Curare with light general anesthesia now presents another choice. Our experience with the cases of the first group led to the conclusion that the order of choice of anesthesia is as follows: spinal anesthesia, light general anesthesia with curare and deep general anesthesia or other methods. Spinal anesthesia is still superior to any other methods for this type of surgery. Its simplicity, reliability and efficiency remain unsurpassed. If light general anesthesia with curare is compared to deep anesthesia or other technics, it is our impression that the more favorable effect on the patient and the greater ease of administration make the former method preferable to the latter.

The problem of managing the cases in which the spinal anesthesia is wearing off and the intra-abdominal surgery is continuing has been simplified by the introduction of curare. In the cases in which a spinal anesthetic does not provide sufficient relaxation with the aid of a light general anesthetic, either curare must be added or the light general anesthesia must be deepened to obtain relaxation. The obvious advantages of the method employing curare are that the depression of the general condition of the patient is avoided, with a recovery period that is shorter and freer from complications, and that control of the problem is obtained with relative ease.

The use of curare in the anesthesia of poor-risk patients introduces a new variation of balanced anesthesia. By the use of light cyclopropane anesthesia with small doses of curare, this method employs the principle of balanced spinal anesthesia described by Wiggin.[17] In both methods, two agents are administered in small amounts and are well tolerated by the handicapped patient. Since these agents act on different structures — the central nervous system and the neuromuscular junction and, in the balanced spinal anesthesia, the central nervous and peripheral nervous systems — their anesthetic effect is cumulative. Thus, satisfactory anesthesia can be accomplished by their balanced use with small doses that, if used alone, would be insufficient. The possible systemic effect of these low dosages is apparently not cumulative and seems to remain below the point where it would affect the general condition of the poor-risk patient to any appreciable extent. The administration of light cyclopropane anesthesia with curare or in balanced spinal anesthesia is similarly accompanied by the simultaneous administration of high percentages of oxygen and fluid therapy. This new variation of balanced anesthesia seems to be a valuable method for these types of patients.

The use of curare to facilitate intratracheal intubation adds another method to the various technics of preparing patients for intubation. The advantage of this procedure is that it allows the anesthesiologist to use a light level of general anesthesia and to obtain complete relaxation in a relatively short time. The possible respiratory embarrassment following intubation is a disadvantage.

Postoperative complications that are respiratory in origin emphasize the importance of the physiologic control of respiration during the operation and the necessity of the same careful supervision of the patients who are under the effect of curare in the postoperative period.

270 Commonwealth Avenue

References

1. Griffith, H. R., and Johnson, G. E. Use of curare in general anesthesia. *Anesthesiology* **3**:418-420, 1942.
2. Cullen, S. C. Clinical and laboratory observations on use of curare during inhalation anesthesia. *Anesthesiology* **5**:166-173, 1944.
3. Brody, J. Use of curare in sodium pentothal-nitrous oxide-oxygen anesthesia. *Anesthesiology* **6**:381-384, 1945.
4. Cole, F. Use of curare in anesthesia: a review of 100 cases. *Anesthesiology* **6**:48-56, 1945.
5. Whitacre, R. J., and Fisher, A. J. Clinical observations on use of curare in anesthesia. *Anesthesiology* **6**:124-130, 1945. *Idem.* Use of curare in anesthesia. *Ohio State M. J.* **40**:1155-1157, 1944.
6. Waters, R. M. Nitrous oxide-oxygen and curare. *Anesthesiology* **5**: 618, 1944.
7. Adams, R. C. Curare as aid to relaxation in anesthesia. *S. Clin. North America* **25**:735-739, 1945.
8. Griffith, H. R. Use of curare in anaesthesia and for other clinical purposes. *Canad. M. A. J.* **50**:144-147, 1944.
9. Cullen, S. C. Curare in anesthesia. *Surgery* **18**:45-47, 1945.
10. Gross, E. G., and Cullen, S. C. Effects of anesthetic agents on muscular contraction. *J. Pharmacol. & Exper. Therap.* **78**:358-365, 1943.
11. Ruskin, A., Ewalt, J., and Decherd, G. M., Jr. Electrocardiogram of curarized human patients. *Dis. Nerv. System* **4**:335-341, 1943.
12. Gross, E. G., and Cullen, S. C. Action of curare on smooth muscle of small intestine and on blood pressure. *Anesthesiology* **6**:231-238, 1945.
13. Fegler, J. Action of curare on respiratory center. *J. Physiol.* **100**: 417-422, 1942.
14. Cole, F. New lethal dose of curare, with some observations on pathology produced by large doses. *Anesthesiology* **7**:190-197, 1946.
15. Schmidt, C. F. Recent developments in respiratory physiology related to anesthesia. *Anesthesiology* **6**:113-123, 1945.
16. Griffith, H. R. Physiological and clinical action of curare. *Anesth. & Analg.* **25**:45-51, 1946.
17. Wiggin, S. C. Balanced spinal anesthesia. *Anesth. & Analg.* **18**: 193-195, 1939.

CARCINOMA OF THE BREAST

A Review of the First Three Years' Experience in the Cancer Section of the Westfield State Sanatorium

FREDERICK S. HOPKINS, M.D.,* AND NICHOLAS EGNATZ, M.D.†

WESTFIELD, MASSACHUSETTS

TWO hundred and fifty-eight patients with carcinoma of the breast were seen in the Cancer Section of the Westfield State Sanatorium in its first three years, 1938 through 1940. In 70 cases a radical operation was done in hope of cure. Simple mastectomies were performed in 7 cases, whereas 138 patients were referred after having been treated at other hospitals.

Thanks to an extremely efficient social-service department, all these patients have been followed. All except 4 of the surviving patients who were operated on are still being regularly examined at the clinic, and the others have been visited by one of the social workers.

Our routine procedure at the time of the first visit of a patient with suspected cancer of the breast consisted in x-ray films of the chest, as well as the upper ends of the humeri, the skull, the spine and the pelvis, including the upper ends of the femurs. Unsuspected metastases have been found in several cases that would otherwise have been deemed operable. Other contraindications that we have followed are fixed, matted lymph nodes in the axilla and definite inflammatory carcinoma. If there is any suspicion of involvement of the supraclavicular nodes, a biopsy is done first. In this series the patient's general condition has not been considered a contraindication to operation, although most of the simple mastectomies were done because of poor physical condition. There were deaths in 3 cases after radical operations, however, and 1 fatal case following a simple mastectomy — all in patients over seventy years of age and in poor physical condition. Johnson and Lombard[1] have shown that the operative mortality in cancer is directly proportional to age. Since then we have more carefully evaluated patients in the older age group and refer them for radiation treatment unless we believe that they have a life expectancy of at least five years. After this procedure had been adopted, there were no postoperative deaths.

The operations were performed by thirteen members of the visiting and resident staffs. Most operations began with a local excision of the tumor and a frozen section to confirm the diagnosis. A formalin-soaked sponge was placed in the cavity before suturing, and the wound was sealed with collodion and gauze. The usual incision was of the Rodman–Greenough type. We believe, however, that the important feature is to make the incisions include an area of skin at least as wide as the breast and with the tumor at least 5 cm. from the incision. After the pectoral muscles have been divided at their insertions, a meticulous dissection of the axilla is made, all areolar tissue being removed from the axillary vein. The upper rectus fascia is removed with the breast, muscles and axillary contents. Wide undercutting usually permits closure without grafting. The value of thorough, extensive dissection is clearly illustrated by the report of Haagensen and Stout,[2] who found no statistically significant difference in the results of various types of radical mastectomies. But the cure rate was in direct proportion to the duration of the operation. The rate for procedures lasting less than an hour was 28.6 per cent, whereas for each successive hour of operating time it was 35.3, 34.3, 43.7 and 56.3 per cent respectively.

Preoperative x-ray treatment was not used, but all patients with axillary metastases were given postoperative radiation. The usual dose was 7200 r. Four portals were employed, 1800 r being given to a 10-by-15-cm. supraclavicular area, to a 10-by-10-cm. axillary area, to a 10-by-15-cm. posterior axillary area and to a 15-by-15-cm. area on the anterior chest wall. The other factors were a constant potential of 200 kilovolts, a wave length of 0.16 angstrom, a distance of 50 cm., and a filter of 1 mm. aluminum and 0.5 mm. copper. Women who were still menstruating were offered ovarian radiation, which most of them accepted.

In the determination of results, operative deaths and patients alive with recurrence were classed as failures. Of the 70 patients who had radical operations 30, or 43 per cent, are living and well without evidence of cancer. Of the 45 cases with axillary metastases 14, or 31 per cent, are considered five-year cures. When no involvement of the axillary lymph nodes was found 16 of 25 patients, or 64 per cent, are living and well (Table 1). Three of the deaths, however, were from other causes without evidence of recurrence. With the elimination of these cases the cure rate is raised to 73 per cent. Nine of the 70 patients with radical operations had had either a simple mastectomy or local excision of a tumor before being referred to us. Of these only 3 cases are considered clinical cures. Five patients showed no evidence of axillary metastases. If these are eliminated, as well as those dying

*Director, Cancer Section, Westfield State Sanatorium; visiting surgeon, Springfield Hospital.

†Formerly, assistant superintendent, Cancer Section, Westfield State Sanatorium.

of other causes without recurrence, the five-year cure rate is 89 per cent for patients without involvement of the lymph nodes, 34 per cent for those with lymph-node involvement and 50 per cent for the whole series. We are convinced that the complete radical operation should be done at the time of the first surgical approach to a cancer of the breast.

Three of the 6 patients on whom simple mastectomies were performed are without present evidence of cancer. We do not believe, however, that simple mastectomies should be done with the expectation of cure.

Table 2 presents the comparative results of a few previous studies. In the series at the Massachusetts General Hospital[3] and in our series all recurrences — even those after five years — and operative deaths are considered failures. Deaths from intercurrent disease are excluded. The figures in the Mayo Clinic[4] series represent five-year survivals. The figures at Presbyterian Hospital[2] represent the clinical cures divided by the number of operations.

Ten, or 14 per cent, of the patients in whom radical mastectomies had been performed developed local recurrences, some of them after five years. Other published series have varied in this factor from Rodman's[5] 2.2 per cent to Haagensen and Stout's[2] 22.8 per cent. There were no recurrences of cancer in the axilla in our series. An analysis of our cases disclosed that in all but 2 in which neoplasm reappeared in the operative field there were features of questionable operability, such as axillary lymph nodes over 2.5 cm. in diameter, all or nearly all lymph nodes involved and signs suggesting a possible inflammatory type. We believe that wide removal of skin minimizes local recurrences, but unless one is too selective in choosing cases for operation a few recurrences are inevitable.

The extent of involvement of the axillary lymph nodes is of great prognostic significance, as shown by Warren and Tompkins[6] in a study of cases from the Massachusetts State Cancer Hospital at Pondville. When all the axillary nodes showed metastases, there were no cures in our series, although one patient lived over five years before developing a recurrence.

We have not considered microscopical grading of sufficient value for routine use. Our pathologist, however, reviewed the slides with the following results. There were 4 cases of Grade I carcinoma, with 75 per cent five-year cures, 31 cases of Grade II, with 48 per cent cures, and 24 cases of Grade III, with 37 per cent cures.

One hundred and twenty-five patients in whom mastectomies had been performed elsewhere were followed in our clinic. In a few, radical operations had been performed at the Massachusetts State Cancer Hospital in Pondville, and the patients had been transferred merely for routine examination. Most of them had been operated on in various local hospitals and had been referred to us for x-ray treatment.

TABLE 1. *Results of Radical Mastectomy in 70 Cases at Westfield State Sanatorium.*

Type of Case	Patients Well 5–8 Years after Operation		Postoperative Deaths		Patients Alive with Cancer		Patients Dead with Cancer		Patients Dying of Other Causes	
	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage
No metastases to lymph nodes	16	64	1	4	1	4	4	16	3	12
Metastases to lymph nodes	14	31	2	4	3	7	26	57	0	0
Totals	30		3		4		30		3	
Averages		43		4		6		43		4

TABLE 2. *Five-Year Clinical Cures following Radical Mastectomy.*

Type of Case	All Westfield Cases		Cases with Primary Operation at Westfield		Westfield Cases with Operation Elsewhere		Massachusetts General Hospital[3]		Mayo Clinic[4]		Presbyterian Hospital[2]		Hartford Hospital[5]	
	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage	No.	Percentage
No metastases to lymph nodes	22	73	17	89	42	24	60	70	1634	74	237	61	134	69
Metastases to lymph nodes	45	31	41	34	61	16	114	31	2913	28	385	21	216	24
Totals	67		58		103†		174		4547		622		350	
Averages		45		50		18		45		45		36 (40*)		42 (45*)

*Eliminating untraced patients and those dying of other causes.

†The status of the lymph nodes was unknown in 22 additional cases in this group.

Twenty-two, or 18 per cent, of these 125 cases were considered five-year clinical cures. Of the 42 cases without evidence of axillary metastases 10, or 24 per cent, were apparently without recurrence, whereas of the 61 with extension to the lymph nodes only 10, or 16 per cent, were without evidence of carcinoma after five years. There were 22 cases in which there was no definite information concerning the status of the lymph nodes. Only 4, or 3 per cent, of the entire group developed local recurrences.

Forty-seven patients were considered inoperable when first seen and were treated by x-ray only. Of these, one is regarded as a five-year clinical cure and 2 have passed the five-year mark but have developed recurrences. The average length of life in this group was thirty-six months from the onset of the disease. These cases cannot be compared with Daland's[7] series of untreated cases in which the average length of life was forty and a half months, because only the advanced cases were treated exclusively by x-ray therapy.

Haagensen and Stout[8] have made a careful study of the criteria of inoperability and of factors of poor prognostic significance. The following are considered definite contraindications to operation: distant metastases, inflammatory type of carcinoma, supraclavicular metastases, edema of the arm, intercostal or parasternal nodules, satellite nodules in the skin over the breast, extensive edema of the skin over the breast and carcinoma developing during pregnancy or lactation. They obtained no cures in this group, which they call "categorically inoperable." Other factors of such poor prognostic significance that the presence of any two is regarded as a contraindication to operation include ulceration of the skin, limited edema of the skin (less than a third), fixation of the tumor to the chest wall, axillary lymph nodes measuring 2.5 cm. or more in the transverse diameter and proved to contain metastases by biopsy and fixation of axillary lymph nodes to the skin or the deep structures of the axilla, with the nodes proved to contain metastases by biopsy.

Although we have always considered inflammatory carcinoma to be a contraindication to operation, there was 1 operative case that was apparently of the inflammatory type. This promptly recurred. Two patients had redness of the skin and slight local heat. Each had some other feature of questionable operability. One of these is living and well. In 1 patient the axillary lymph nodes over 2.5 cm. in diameter with questionable fixation were found to be merely inflammatory, and there is no evidence of recurrence. The 12 other cases with various combinations of ulceration, limited edema, fixation to the chest wall, satellite skin nodules, axillary lymph nodes over 2.5 cm. in diameter, questionable fixation of nodes, preoperative edema of the arm or redness of skin or local heat are all considered failures. The other factors mentioned by Haagensen and Stout did not occur in this group.

A thorough statistical review of 570 cases of carcinoma of the breast with radical mastectomies in 350 has recently been made by Wells,[9] of the Hartford Hospital. Two of the 3 cases in which cancer developed during pregnancy or lactation were classified as ten-year cures. In the group in which two factors of poor prognostic significance were considered a contraindication to operation there were a few scattered cures in both series except when either multiple tumors or skin edema was combined with other factors. In the group that would be classified as inoperable by Haagensen and Stout,[8] Wells[9] had 57 cases of which 8, or 14 per cent, were considered five-year clinical cures, and 7 apparently permanent cures. Harrington,[4] of the Mayo Clinic, reported 99 operated cases of cancer of the breast developing during pregnancy or lactation, with axillary metastases in 84.8 per cent. In this group the five-year and ten-year survivals were 7.7 and 3.1 per cent, whereas in those without axillary metastases the figures were 57.1 and 38.5 per cent respectively.

Discussion

Although this is too small a series to be statistically conclusive, we believe that it emphasizes certain important facts. One cannot repeat too often that a thorough radical operation will cure most cases of cancer of the breast if performed before there are axillary metastases. In our cases in which the lymph nodes were already involved 31 per cent of patients are alive without evidence of cancer. A total five-year salvage of 43 per cent in all our radical operations is encouraging. This figure could be improved slightly by more strict adherence to Haagensen and Stout's criteria. We believe, however, that every case in which there is a possibility of cure should have the benefit of operation. We accordingly operate on many poor-risk patients except those with an estimated life expectancy of less than five years. Enough good results have been obtained in patients developing cancer during pregnancy or lactation to justify the attempt. Unless large axillary lymph nodes are firmly fixed, operation might obtain a good result, and the case should certainly not be classified as inoperable without a biopsy of the nodes. When the finding of satellite nodules, multiple tumors or skin edema is combined with other unfavorable features, there is too slight a possibility of cure to warrant operation. We agree that distant or supraclavicular metastases, inflammatory carcinoma, preoperative edema of the arm, intercostal or parasternal nodules and extensive edema of the skin are contraindications to operation. The other features, such as redness, ulceration or limited edema of the skin, fixation of the tumor to the chest wall and large or adherent axillary lymph nodes showing

cancer, are factors indicating a poor prognosis. The percentage of axillary lymph nodes showing metastasis and the microscopical grade of the tumor are also of valuable prognostic significance. It is dangerous to rely on the clinical impression regarding the involvement of the nodes. In 11 cases the pathologist found metastases that were not diagnosed clinically, whereas in 3 the nodes were considered involved but no metastases were found.

This series does not permit any significant evaluation of x-ray treatment. The patients with involvement of the axillary lymph nodes gave us slightly better results than those in most of the published statistics, and all of them were given postoperative radiation. We do not believe, however, that the results can be attributed to the radiation. All except one of the patients who developed local recurrences had had x-ray treatment. We believe that the patients who received only palliative x-ray treatment were made much more comfortable and that there was some prolongation of life. We have recently omitted routine postoperative x-ray treatment of patients with axillary metastases.

Summary

Two hundred and fifty-eight patients with cancer of the breast seen at the Cancer Section of the Westfield State Sanatorium over five years ago are reviewed. Fifty-nine, or 23 per cent, were considered five-year clinical cures. Thirty, or 43 per cent, of the 70 patients who had radical mastectomies at Westfield are alive without evidence of recurrence five to eight years following operation. Ten, or 14.5 per cent, of this group had local recurrences. There was no case of recurrence in the axilla. Twenty-two, or 18 per cent, of the group that we followed who had had radical mastectomies elsewhere are apparently cured.

The observance of the operative criteria proposed by Haagensen and Stout would improve the figures of five-year survivals but would allow an occasional patient to receive only palliative treatment when there was a possibility of obtaining a cure. These criteria are of prognostic value.

The percentage of lymph-node involvement and the microscopical grade of the tumor are of aid in prognosis.

X-ray treatment is of great help in making the patient more comfortable.

The value of a complete radical operation at the time of the first surgical approach to cancer of the breast is illustrated by the fact that whereas our percentages of five-year clinical cure were 73 per cent with negative nodes, 31 per cent with axillary metastases and 45 per cent for the series, by the elimination of patients who had previous operations the corresponding percentages were 89, 35 and 50 per cent.

References

1. Johnson, A. S., and Lombard, H. L. Estimation of operative risk in patients with cancer. *New Eng. J. Med.* **224**:759-762, 1941.
2. Haagensen, C. D., and Stout, A. P. Carcinoma of breast: results of treatment. *Ann. Surg.* **116**:801-815, 1942.
3. Simmons, C., Taylor, G. W., and Welch, C. E. Carcinoma of breast: end results: Massachusetts General Hospital 1930, 1931, and 1932. *Surg., Gynec. & Obst.* **69**:171-177, 1939.
4. Harrington, S. W. Results of radical mastectomy in 5026 cases of carcinoma of breast: various clinical and pathologic factors which influence prognosis. *Pennsylvania M. J.* **43**:413-427, 1940.
5. Rodman, J. S. Skin removal in radical breast amputation. *Ann. Surg.* **118**:694-705, 1943.
6. Warren, S., and Tompkins, V. N. Significance of extent of axillary metastases in carcinoma of female breast. *Surg., Gynec. & Obst.* **76**:327-330, 1943.
7. Daland, E. M. Untreated cancer of breast. *Surg., Gynec. & Obst.* **44**:264-268, 1927.
8. Haagensen, C. D., and Stout, A. P. Carcinoma of breast: criteria of operability. *Ann. Surg.* **118**:1032-1051, 1943.
9. Wells, D. B. Unpublished data.

MULTIPLE CONGENITAL DEFECTS FOLLOWING MATERNAL VARICELLA*

Report of a Case

EUGENE G. LAFORET, A.B.,† AND CHARLES L. LYNCH, JR., B.S.‡

CAMBRIDGE AND BOSTON

INVESTIGATION of the factors responsible for congenital malformations received tremendous impetus in 1941 with the classic report by Gregg,[1] of Australia, of a series of cases in which maternal rubella was followed by a variety of anomalies in the offspring, particularly such ocular defects as cataract. Previously, it had been generally accepted that malformations do not result from environmental factors that operate for the first time after fertilization.[2] Attention, therefore, had been directed chiefly at possible preconceptual causes. The studies of Gregg[1] and of numerous subsequent workers, however, emphasized the necessity of according careful consideration to environmental conditions obtaining after the fetus has become established.

The significance of this newly adopted approach to the problem of congenital malformations is already well recognized, and a voluminous literature has sprung up since the initial publication from Australia. Considered from the aspect of preventive pediatrics, therefore, the potentialities of continued work in this field are gratifying.

The maternal virus disease that thus far appears to be the most frequent offender is rubella. In 1945 Conte, McCammon and Christie[3] collected 136 cases of congenital malformation with a definite history of maternal prenatal virus infection, in all but 2 of which rubella was the associated disease, a case of mumps and one of influenza constituting the exceptions.[4] On the basis of analogy, however, the suspicion is growing that the incidence of congenital malformation following other maternal prenatal virus infections parallels that associated with rubella. This is suggested by Fox and Bortin,[5] who recommend more extensive investigation of the possible relation of congenital malformations to any of the virus diseases that occur during gestation. In the following case maternal varicella occurring in the eighth week of pregnancy was followed by delivery of a child with extensive congenital defects.

CASE REPORT

A 6-hour-old infant (B.F.H. 90816) was admitted to the hospital on October 27, 1945, because the attending physician had detected an anomaly of the right leg. The mother, a 23-year-old housewife, had had pertussis, rubeola and asthma in childhood; at the age of 7 or 8 years she had been unable to bear weight on her legs and was presumed to have had rickets at that time. So far as could be ascertained, there was no family history, either maternal or paternal, of congenital anomalies. The mother had contracted varicella in the 8th week of pregnancy, when she was "covered from head to foot" with lesions and had a temperature of 102°F. for two weeks. The diagnosis of varicella was well established, since the case had apparently been a classic one. A 3-year-old female sibling of the patient had also had varicella synchronously with the mother. The course of the pregnancy had been normal except for an occasional whitish vaginal discharge that was more marked in the morning. The gestation proceeded to term, delivery being by vertex and spontaneous.

Physical examination revealed a poorly developed, normally nourished infant. The skin was pinkish and normal except for several well defined reddish pigmented areas, 3 to 5 mm. in diameter, on the medial aspect of the left thigh and leg. The head was round and regular. The eyes showed only questionable reaction to light. The scleras and conjunctivas were clear. There was no nasal discharge. Otoscopic examination disclosed normal tympanic membranes bilaterally. The oral cavity and oropharynx were normal. There was no nuchal rigidity or cervical lymphadenopathy. The lungs were resonant and clear. The heart was not enlarged to percussion, and no abnormality of rate, rhythm or sounds was detected. The abdomen was soft. The liver was palpated three fingerbreadths below the right costal margin. The spleen could not be felt. No costovertebral swelling or other abdominal masses were discovered. Grossly the external genitalia appeared normally developed except for an undescended left testicle, but urine constantly dribbled throughout the examination. The anal sphincter, which was at the level of the buttocks, was relaxed and widely patent, presenting a continuous discharge of fecal material. The extremities were normal except for the right lower leg, which was thin and underdeveloped in comparison with its mate, and a right talipes equinovarus; the toes of the right foot were underdeveloped, the terminal phalanges being represented only by small horny pegs, and the great toe was in abnormal apposition. The muscular atrophy of the right leg extended to the gluteal region. The deep tendon reflexes were physiologic except for an absent knee jerk on the right and an unelicitable Achilles reflex on the right. In the lumbar region there was a longitudinal depression, 3 cm. in length and 0.5 cm. in depth, that was free of discharge. Routine urinalysis and blood counts on admission were not remarkable.

X-ray studies on October 29 revealed no evidence of increased intracranial pressure or of any abnormality of the vertebral column. A chest plate was normal. Films of the right leg and foot were reported as follows:

> The right lower extremity is markedly underdeveloped. The bone is retarded in development, and the soft tissues have an abnormal appearance. The foot is particularly deformed, the 4th and 5th toes having only a basal phalanx and no middle or end phalanges. The size of the individual bone is but a fraction of that of a normal one. This is obviously a congenital anomaly of a developmental character.

The right leg showed no improvement and apparently was not growing. Actively, it could not be fully extended at the knee, and even passively could not be fully flexed at the hip. Measurement on December 10 revealed it to be 2 cm. shorter than the left.

After two previous attempts at lumbar puncture had resulted in bloody taps, a third on December 19 was satisfactory; analysis was essentially normal except for a total protein of 160 mg. per 100 cc. Bilateral subdural taps were also done on this date and disclosed a large amount of clear fluid, also with a high protein content (117 mg. per 100 cc.).

On January 2, 1946, a pneumoencephalogram was performed, 30 cc. of air being injected over a period of 2 hours after the withdrawal of 35 cc. of cerebrospinal fluid. Large,

*From the Boston Floating Hospital (pediatric unit of the New England Medical Center).

†Fourth-year medical student, Tufts College Medical School; junior intern, Cambridge City Hospital.

‡Fourth-year medical student, Tufts College Medical School; junior intern, St. Margaret's Hospital.

dilated lateral ventricles were visualized that were highly suggestive of hydrocephalus internus. Some air was also observed to be trapped in the region of the cisterna magna, which appeared much larger than normal. Briefly, the films were consistent with generalized cortical atrophy, hypoplasia or aplasia of the cerebellum and, possibly, internal hydrocephalus.

Lumbar puncture was repeated on January 3, and analysis of the cerebrospinal fluid showed a total protein of 234 mg. per 100 cc.

The temperature began to exhibit wide fluctuations on January 4 and 3 days later reached a maximum in excess of 108°F. Enemas, clyses, sponges and the ingestion of acetylsalicylic acid were followed by a reduction in temperature. The infant was having fourteen loose green stools a day by January 9 and was put on fluids and sulfadiazine. On January 11 the red-cell count was 2,560,000, and the white-cell count 6600; the temperature became more regular, and the diarrhea showed signs of abating. The intravenous administration of 50 cc. of whole blood, however, failed to effect an improvement in the red-cell count.

On January 14 the patient developed nuchal rigidity, convulsions, spastic movements of the extremities, opisthotonos and an elevated temperature, without, however, exhibiting bulging fontanels. Cerebrospinal fluid obtained by lumbar puncture was clear, with a total protein of 85 mg. per 100 cc., no leukocytes and a few crenated and noncrenated red cells; culture showed no growth after 72 hours. Symptomatic therapy resulted in significant improvement, and the course was uneventful until February 10, when diarrhea again developed. A site of infection was not found, but routine therapy with fluids and sulfadiazine was again followed by improvement. The weight gain continued to be satisfactory. Fluctuations in temperature, never entirely absent, again became marked, the temperature periodically dropping as low as 93°F.

Re-evaluation of the patient at 4 months of age showed paralysis of the right leg extending to and including both gluteal muscles and no alteration in the talipes equinovarus of the right foot. The left leg was better developed and had more substance, but it was far from normal. The pilonidal sinus was still clearly evident. The lesions on the skin of the left thigh were white, raised and slightly irregular. A severe torticollis to the right was present, and only by force could the head be maintained in normal position. The eyes exhibited continuous lateral nystagmoid movements. Ophthalmoscopic examination revealed bilateral optic atrophy and a peculiar darkish pigmentation of the retinas. On the whole, the patient appeared abnormally quiet and inactive.

A glucose-tolerance test done on April 17 showed the blood sugar to be 89 mg. per 100 cc. fasting, 160 mg. at 30 minutes, 129 mg. at 1 hour, 123 mg. at 2 hours and 127 mg. at 3 hours; no urinary sugar was found during the test period.

Except for the sudden appearance and remission of spasticity, vomiting and bulging fontanels on March 15, not due to meningitis, the course continued uneventfully, and the patient was discharged on April 29 under the supervision of the Social Service Department.

Although a purely pathological diagnosis is not feasible in this case, it may prove interesting to list the defects that may justifiably be considered to have been present: talipes equinovarus, right; paralysis and muscular atrophy, right lower extremity; defective development, toes of right foot; cortical atrophy; hypoplasia or aplasia of cerebellum; ? internal hydrocephalus; bilateral optic atrophy; pilonidal sinus; torticollis to right; cicatricial (? post-varicella) lesions, skin of left lower extremity; undescended testicle, left; and insufficiency of anal and vesical sphincters.

In addition, certain defects of a preponderantly physiologic nature were noted, such as hyperirritability of the central nervous system, poorly functioning thermoregulatory ability and an apparent increased susceptibility to infection.

Discussion

The case presented above is one in which a well authenticated episode of maternal varicella complicating the eighth week of pregnancy was followed by term delivery of an infant with extensive developmental defects. The maternal and paternal family histories were devoid of congenitally malformed offspring. A three-year-old sibling of the patient was normal. Apparently, then, constitutional factors may be minimized as contributing to the etiology of the multiple defects, whereas the possibility is enhanced that the prenatal varicella was the responsible agent. As Conte, McCammon, and Christie[3] point out, however, it is difficult to evaluate the significance of reported cases because it is not known how often virus infections occur without congenital malformations or how often malformations occur without virus infections — in other words, there are no controls for the reported cases. An effort was made to determine the frequency with which maternal gestational varicella was followed by offspring with such severe congenital defects, but in a review of the literature no similar reports could be discovered. At this writing, the case detailed above is apparently the first of its kind to appear in the literature, although we may be unacquainted with pertinent prior papers. In this connection, however, it may be interesting to quote, in toto, a case cited by Conte, McCammon and Christie,[3] together with their comment:

> *Case 7.* J. M., a white boy, was born at term of a 23-year-old mother, who had chickenpox in the second week of her pregnancy. Delivery was normal. His immediate neonatal condition was good. His birth weight was 7 pounds (3,175 gm.). There was no congenital anomaly found in this infant. . . . The varicella occurred in the first month and was not followed by a congenital anomaly in the child. There have been no previous observations made concerning the relationship between this disease and congenital anomalies.

Failure of this infant to demonstrate defects does not necessarily negate or modify the possible propensities of maternal gestational varicella for the production of anomalies. In the first place, the disease was contracted in what was apparently the second week of pregnancy; however, since estimated dates of conception are notoriously inaccurate, it is possible that the mother did not actually become pregnant until after the disease had been experienced; Swan and Tostevin[6] remark the absence of congenital defects following rubella that occurs just before pregnancy. Again, the third principle of Stockard[7] — cited below — may have been operative. A final explanation, which admittedly cannot be definitely excluded at present, is that maternal varicella bears only a coincidental and not an etiologic relation to subsequent infantile anomalies.

More or less incidentally in a paper concerned chiefly with the relation of maternal gestational rubella to congenital defects, Swan and Tostevin[6] mention 2 cases of pregnancy complicated by varicella, in both of which the mothers contracted the disease in the seventh month. One of the infants born subsequently was normal; the other had a nevus of the scalp, and the x-ray findings were suggestive of a cardiac defect — an enlarged heart, a small aorta and configurations indicating right

ventricular preponderance. In both cases the disease occurred well beyond the period (first trimester) when congenital defects are most to be feared, and in the significant case the defects were neither severe nor extensive.

Carefully to be distinguished from congenital anomalies following maternal varicella (teratogenic varicella) is congenital varicella, in which the pathogenesis of the disease in utero closely parallels the course it pursues in its better known guise as an almost inevitable but relatively benign childhood exanthem. There have been numerous references to the occurrence of varicella in the newborn,[8–21] some better substantiated than others; in these cases the mothers contracted the disease near term and presumably transmitted the virus transplacentally, the child either being born with a fully developed vesicular eruption or developing it so soon after birth that sources of infection other than intrauterine could be discounted.

To cause severe developmental defects varicella or other virus disease must apparently occur in the first trimester of pregnancy. Goodpasture believes that this susceptibility during early pregnancy may be due to the fact that young and relatively undifferentiated cells are a more propitious medium than mature cells.

In this connection, three experimental conclusions of Stockard[7] cited by Swan and Tostevin[6] are presented as being particularly applicable:

> The type of abnormality is determined by the particular developmental "moment" at which the noxa acts. At different periods in the development of the ovum, certain primordia are undergoing rapid proliferation, and may be thought of as developing at a rate entirely in excess of the general developmental rate of the embryo. At such periods these primordia are peculiarly susceptible to unfavourable influences, while only slight or no ill effects may be suffered by the embryo as a whole.
>
> The earlier the arrest the more numerous will be the types of defect found, and the later the arrest the more limited the variety of deformities, since there are fewer organs to be affected during their rapidly proliferating primary stages.
>
> If development is arrested or retarded at a stage when no unusually rapid changes are taking place, a comparatively quiescent moment during which all parts are developing, but during which no particular or important part is proliferating at an excessively high rate, the embryo may escape injury.

Regarding the last conclusion of Stockard, Swan and Tostevin state: "If such 'moments of indifference,' as Stockard calls them, occurred in the earlier months of pregnancy, they would serve to account for the (so far) rare cases in which mothers have contracted rubella during these months and yet have given birth to apparently normal infants."

Perhaps the first reference to congenital anomalies following maternal virus disease is the rather esoteric observation attributed by Lynch[22] to Watson,[23] who, in a paper published in 1749, stated that the fetus "was liable to be infected [with variola] at a very different time and in a very different manner from the mother." The potentially teratogenic aspects of maternal rubella are receiving increasing emphasis and are well known. Congenital anomalies have been reported following mumps[4, 6] herpes zoster,[6] rubeola[6] and influenza.[4] Conte, McCammon and Christie,[3] after reviewing the literature, could find no reference to congenital malformation subsequent to maternal varicella, although the case reported above and the most recent survey by Swan and Tostevin[6] indicate that such an occurrence is possible. Waaler[24] has discussed 8 cases of acute anterior poliomyelitis in pregnant women between eighteen and thirty-eight years of age, without the occurrence of fetal malformations. Nevertheless, in a review article concerned primarily with maternal rubella, Aycock and Ingalls[25] incidentally mention recent observations relative to poliomyelitis complicating gestation, and conclude that the risk to the fetus in maternal poliomyelitis is, as in German measles, high if the disease occurs in the first three months of pregnancy and less in later months. It is not clear, however, to what extent the hazard to the fetus is the result of paralysis in the mother. Conte, McCammon, and Christie[3] have tentatively exonerated epidemic encephalitis, although not denying the possibility that it, too, may act as a teratogen.

Although not a virus disease, scarlet fever concurrent with pregnancy has occasionally been followed by developmental defects, such as congenital obliteration of the bile ducts in the case reported by Swan and Tostevin.[6]

Summary

A case of multiple congenital defects following maternal varicella is reported. Present opinion on the pathogenesis of anomalies associated with maternal prenatal virus infection is reviewed. The possible teratogenic propensities of maternal virus diseases occurring early in pregnancy are emphasized.

References

1. Gregg, N. M. Congenital cataract following German measles in mother. *Tr. Ophth. Soc. Australia* 3:35-46, 1942.
2. Murphy, D. P. *Congenital Malformations: A study of parental characteristics with special reference to the reproductive process.* 98 pp. Philadelphia: University of Pennsylvania Press, 1940. P. 97.
3. Conte, W. R., McCammon, C. S., and Christie, A. Congenital defects following maternal rubella. *Am. J. Dis. Child* 70:301-306, 1945.
4. Swan, C., Tostevin, A. L., Moore, B., Mayo, H., and Barham Black, G. H. Congenital defects in infants following infectious diseases during pregnancy, with special reference to relationship between German measles and cataract, deaf-mutism, heart disease and microcephaly, and to period of pregnancy in which occurrence of rubella is followed by congenital abnormalities. *M. J. Australia* 2:201-210, 1943.
5. Fox, M. J., and Bortin, M. M. Rubella in pregnancy causing malformations in newborn. *J. A. M. A.* 130:568, 1946.
6. Swan, C., and Tostevin, A. L. Congenital abnormalities in infants followine infectious diseases during pregnancy, with special reference to rubella: third series of cases. *M. J. Australia* 1:645-659, 1946.
7. Stockard, C. R. Developmental rate and structural expression: experimental study of twins, "double monsters" and single deformities, and interaction among embryonic organs during their origin and development. *Am. J. Anat.* 28:115, 1921.
8. Hubbard, T. W. Varicella occurring in infant twenty-four hours after birth. *Brit. M. J.* 1:822, 1878.
9. Grindon, J. Apparent case of varicella in utero. *J. Cutan. Dis.* 19: 237, 1901.
10. Pridham, F. C. Chicken-pox during intrauterine life. *Brit. M. J.* 1: 1054, 1913.

11. Senator. Cited by Schamberg, J. F. Chickenpox. In *Nelson Loose-Leaf Living Medicine*. Vol. 1. New York: Thomas Nelson & Sons, 1926. Pp. 529-544.
12. Ivenskaya, E. A. Chickenpox in premature children. *J. izuch. rann. detsk. vozr.* 9:504-508, 1929.
13. Troetskiy, A. Y. Course of chickenpox in nurslings. *J. rann. detsk. vozr.* 12:391-395, 1932.
14. Smits, J. W. Herpes zoster en varicellen. *Nederl. tijdschr. v. geneesk.* 76:1708, 1932.
15. Cosgrave, A. K., and Samuel, J. Case of congenital chicken-pox. *Malayan M. J.* 9:68, 1934.
16. Henderson, W. B. Chickenpox in eight-day-old infant. *J. Pediat.* 4:668-670, 1934.
17. Baron, F. Un cas de varicelle mortelle chez le nouveau-né par contagion maternelle. *Bull. Soc. d'obst. et de gynéc.* 24:65, 1935.
18. Mitchell, G. A. Cited by Shuman.[20]
19. Campbell, E. P. Chickenpox in twelve day old infant. *Am. J. Dis. Child.* 57:1408-1410, 1939.
20. Shuman, H. H. Varicella in newborn. *Am. J. Dis. Child.* 58:564-570, 1939.
21. Oppenheimer, E. H. Congenital chickenpox with disseminated visceral lesions. *Bull. Johns Hopkins Hosp.* 74:240-250, 1944.
22. Lynch, F. W. Dermatologic conditions of fetus, with particular reference to variola and vaccinia. *Arch. Dermat. & Syph.* 26:997-1019, 1932.
23. Watson, W. Some accounts of fetus in utero, being differently affected by small pox. *Phil. Tr.* (London) 46:693, 1749.
24. Waaler, E. Acute anterior poliomyelitis complicating pregnancy. *Acta med. Scandinav.* 123:207-218, 1946.
25. Aycock, W. L., and Ingalls, T. H. Maternal disease as principle in epidemiology of congenital anomalies. *Am. J. M. Sc.* 212:366-379, 1946.

MEDICAL PROGRESS

EFFECTS OF PROTEIN DEFICIENCY ON THE PREGNANT WOMAN AND FETUS AND ON THE INFANT AND CHILD (Concluded)*

HAROLD C. STUART, M.D.†

BOSTON

PROTEIN DURING INFANCY AND CHILDHOOD

Requirements

The primary function of protein in the diet is to provide the amino acids that are essential for the synthesis of tissue proteins characteristic of the species. In normal adults, new tissues are required only for replacement or maintenance. Disease and trauma may cause a rapid loss of nitrogen and greatly increase the need for protein at any age. In infants and children three additional factors must be considered. The young person differs from the adult in that he is immature, he is small, and he is growing.

For the most part, infants and children utilize protein well, but normal infants and especially premature infants need protein in a physical form that their digestive tracts can readily assimilate. Levine,[35] in a recent review, cited an example of the influence of immaturity on protein needs. The premature infant has difficulty digesting and absorbing fat and tends preferentially to use protein, as well as carbohydrate, to provide energy, thus increasing protein requirements. Although immaturity undoubtedly increases the margin that must be provided over and above actual tissue requirements, this characteristic of early life is not a major one in determining total protein needs.

Body size influences to some degree the amount of protein that must be provided when requirements are considered on the basis of unit of body mass. The relation of total maintenance or basal needs to body size is not a direct one of straight-line progression, and hence the basal needs are not the same per kilogram of body weight irrespective of size or age. This is apparently due to a relation between the basal caloric and protein requirements. It is well known that the smaller the animal, the higher the energy requirement on the basis of body weight. This need is more constant when based on a unit of surface area, which is relatively greater, the smaller the body mass. Hegsted[36] has pointed out that the protein requirement for maintenance is much more closely correlated with basal energy requirement than with body size. This is understandable since a high basal metabolic rate is associated with a high catabolism, and more materials are therefore required for anabolism. Total protein needs per kilogram of body weight are much higher in infancy than in childhood and somewhat higher in childhood than in adolescence; part of this difference, although as yet an undetermined one, is undoubtedly due to the relation of maintenance need to body size.

The influence of growth on protein requirements in early life is the principal effect with which this discussion is concerned. Levine[35] points out that in infancy and childhood both the quality and the quantity of dietary protein must be adequate to cover growth requirements as well as maintenance needs, under which he includes the allowance for fecal loss. This loss averages between 10 and 15 per cent of the total protein at all ages but varies with the type and amount of protein food consumed and with the functioning of the digestive system. He emphasizes the fact that protein requirements are greatly influenced by the adequacy of the caloric intake.

Several studies on animals have shown that normal growth of the young depends on the provision of suitable proteins and that quantitatively equal amounts of different proteins result in different rates of growth depending on the biologic value of the

*From the Department of Maternal and Child Health, Harvard School of Public Health.
This review was prepared for and presented in part at "A Symposium on Body Proteins" at the celebration of the one hundredth anniversary of the University of Buffalo, September 27, 1946.

†Professor of maternal and child health, Harvard Medical School; head, Department of Maternal and Child Health, Harvard School of Public Health; physician; Children's and Infants' Hospital.

protein. A great body of evidence has been obtained in experience with infant and child feeding that testifies particularly to the unique value of milk proteins but also to the better growth attained on diets liberally provided with milk and other foods from animal sources. These furnish the essential amino acids in suitable proportions and liberal amounts. Nevertheless, Levine concludes, on the basis of evidence from studies on dogs, infants and adults, that positive nitrogen balances of similar magnitude result from equivalent intakes of protein, irrespective of the source of the dietary nitrogen if the protein offered provides all the essential amino acids in adequate amounts.

The quantitative requirements for protein at various ages prior to maturity are increased by an amount necessary to provide for the construction of new tissues laid down in the process of growth. One may arrive at an estimate of the protein requirements for growth in a variety of ways. Nitrogen balance studies on normal subjects, if conducted for sufficient periods, are indicative of the amounts of nitrogen being used for growth. One may also measure the amount of growth and from it estimate the amount of protein required to provide such a gain, but this involves a knowledge of the composition of growth. Since muscle tissue requires the highest deposition of nitrogen and since urinary creatinine excretion is a measure of the gain in muscle tissue, determinations of urinary creatinine excretion are useful in this connection. Clinical studies of growth under known dietary intakes are also useful but must be conducted over long periods and with precise methods both of dietary analyses and of measurements of growth. They throw light on the actual levels of habitual protein intake on which various levels of growth progress may be attained.

The amount of protein necessary to build the new tissues added with growth in any year is a relatively small proportion of the total protein needs when estimated on a daily-intake basis. This assumes that the protein is provided regularly in an otherwise adequate diet so that it is always available for growth. Talbot[37] has recently discussed the theoretical basis for this need and has called attention to the remarkably small daily positive nitrogen balance required to yield a significant growth of protoplasm in the course of a year.

Levine[35] states that, during infancy, the absolute retentions of dietary protein at equivalent and adequate intakes decline from 0.30 gm. of nitrogen per kilogram of body weight daily in the premature infant to 0.15 gm. at five months or older. As pointed out above, recommendations for protein allowances are usually expressed in terms of unit of body mass, — either kilograms or pounds of body weight, — but on this basis the need is influenced to some extent by size and consequently by age. It must not be assumed, therefore, that the difference between the amount recommended on this basis for an infant and that for an adult is entirely due to the rapid growth of the former.

Estimates of protein needs based on theoretical considerations, animal experiments and studies of nitrogen balance, growth and diets in children lead to conflicting conclusions. They have thus far failed to give a clear picture of what the protein requirements are at succeeding ages for optimum growth and health. This is understandable for various reasons. In the first place, it is not known what constitutes optimum growth at any age or for any person. Furthermore, growth in the human being is a slow process, extending over two decades, and children cannot be kept on strictly controlled or known intakes over sufficiently long periods to allow accurate appraisal of growth. Gain in weight is not determined solely by growth, and gain in body length is not a true index of the amount of new tissues laid down.

Human growth progresses continuously from the embryonic period to full physical maturity, but by no means at the same rate at all periods or in equal proportions in different tissues. The protein required for the construction of some tissues is greater than that for others, muscle tissue creating the heaviest demand, and the new tissue components of a young person cannot be analyzed. There are two major cycles of over-all growth separated by a long interval of considerably slower growth. The rapid phase of early infant growth is accompanied by relatively large accumulations of fat in the subcutaneous tissues. The second phase of rapid growth is accompanied by a greater proportionate increase in muscle tissue. Although these changes with time are characteristic of human growth and persons differ only in their magnitudes and their rates of progress, individual differences in all these aspects are so great that variations in protein requirements must be considerable.

The recommendations of the Food and Nutrition Board[9] may be considered to be as satisfactory guides to protein allowances for infants and children as are available at the present time. They must be recognized as applying only to average normal children within the broad age groups specified. Levine[35] has expanded these recommendations to deal more adequately with the subdivisions of the age groups with which they deal. His revised allowances are given in abbreviated form in Table 2. According to these recommendations, the full-term infant under one year of age should be provided a diminishing amount of protein varying from 4.4 to 3.0 gm. per kilogram of body weight. Levine makes the following statement:

> Analysis of available data for infants under one year establishes that these recommended daily allowances of protein . . . are compatible with a normal rate of total weight gain and a ratio of nitrogen retained to total increment of gain which approximates the rising nitrogen content of the body . . . Protein intakes below 2.2 gm. per

kg. in infancy may lead to negative nitrogen balances; levels above those recommended are wasteful since there are no body depots for reserve protein, absorbed amino acids in excess of the needs for growth and maintenance entering interchangeably with fat and carbohydrate into the energy exchange. . . . With further deceleration in the growth curve with increasing age beyond infancy, lower levels of dietary protein per unit of body weight are required for nitrogen retention and protein deposition. The bulk of available evidence indicates that these recommendations [National Research Council allowances] are compatible with normal qualitative and quantitative nutrition as judged by the various means available.

It is generally agreed that if the appetite is normal, approximately 11 to 15 per cent of the calories of the diet should be provided by suitable protein foods at all ages, but a higher percentage may be required under special circumstances. Leitch and Duckworth,[38] who have reviewed this subject thoroughly, recommended allowances that are slightly higher at certain ages but in general are in substantial agreement with those of the Food and Nutrition Board. Youmans[39] makes similar recommendations.

Estimates of the actual amount of protein required by the infant and child at successive ages to provide for optimum growth tend to overlook several important considerations. Protein will be used first to meet the energy need, if this is not fully met from other sources. If the caloric intake is only moderately below the energy need and if reserve sources of calories have been exhausted, the drain on the protein intake for this purpose may be relatively great. Protein will next be used primarily for repair or maintenance, although some growth will undoubtedly take place at the expense of full maintenance and possibly also through the sacrifice of protein-rich body tissues. Only after these needs have been met will protein provide fully for the enlargement of such tissues as muscle. The points that should be stressed, therefore, in the protein requirements of children are that protein intake cannot be considered adequate unless caloric requirement is met, and that the first and most frequent effect of protein deficit is the limitation of growth. The effect of inadequate protein on growth is not easily recognized, and if correction of diet is not made until faulty growth is obvious or until other signs of deficiency are manifest, the child's progress often will have been considerably interfered with. Since it is not known how much constitutes adequacy for any given child at a particular time, a liberal margin of safety must be provided in the amount and quality of protein foods offered, together with an adequate caloric intake, and an otherwise well balanced diet, so that periods of interference with growth due to lack of protein can be avoided.

Youmans[40] has emphasized the importance of acute febrile illnesses as precipitating factors in manifest deficiency states. Infection increases caloric requirements, causes rapid catabolism with nitrogen loss and interferes with normal consumption and utilization of calories and protein, and children are subject to more such illnesses than adults. Furthermore, the emotional disturbances often affecting both mother and child as a result of the latter's illness, often have profound effects on the child's eating habits and attitudes toward food and hence on food consumption. Youmans's contention applies with special force to childhood when he states that protein requirements are greatly increased by most illnesses and that failure to meet these increased needs by careful dietary planning in illness leads to a major number of protein deficiency states. It is difficult and often impossible to maintain nitrogen equilibrium throughout the course of many illnesses, and it is therefore of practical value to provide for storage of nitrogen during convalescence to an amount sufficient to replace damaged tissues and to afford the accelerated growth that usually follows periods of interrupted growth.

TABLE 2. *Recommended Daily Allowances for Protein Expanded for the Growing Period.*

SUBJECTS	AGE	PROTEIN PER KILOGRAM OF BODY WEIGHT
		gm.
Premature infants	1 week to 1 month	6.0–4.4
Premature infants	1 to 3 months	4.4–3.3
Full-term infants	2 days to 3 months	4.4–3.3
All infants	4 months to 1 year	4.0–3.0
Toddlers	1 through 3 years	4.2–2.9
Preschool children	4 through 6 years	3.3–2.5
School children	7 through 9 years	2.6–2.1
School children	10 through 12 years	2.2–1.8
Youths, female	13 through 15 years	1.8–1.5
Youths, male	13 through 15 years	2.0–1.7
Youths, female	16 through 20 years	1.6–1.4
Youths, male	16 through 20 years	2.1–1.7

Effects of Protein Deficiency

It must be pointed out again that protein is rarely, if ever, the sole nutrient that is inadequate in a diet over any long period. The amounts of other essentials present have much to do with the effects of the protein level itself, and growth is known to be interfered with when various dietary essentials are sufficiently restricted. Except in animal experiments, one can rarely assume that poor growth has resulted solely or even primarily from a quantitative inadequacy of protein. There is a great deal of evidence, however, that low protein usually associated with low calories and continued over long periods is a frequent cause of poor growth in childhood. This evidence is derived in part from animal experimentation, in part from studies of the growth of children in tribal or national groups having different dietary habits, in small part from controlled studies of dietary supplements and restrictions, in part from combined dietary and growth studies of groups of children over long periods and more recently from studies of children subjected to inadequate diets as a result of war restrictions. This evidence is still far from complete, but a characteristic picture of the chronically underfed child, particularly regarding calories and protein, is beginning to emerge from it. Space does not permit a thorough review of these

studies, but examples of each are cited; nor does it permit a discussion of the possible mechanisms involved in this slowing of growth when structural food substances are inadequate. The growth impulse is apparently so strong that children continue to grow in height and other skeletal dimensions while losing both fat and muscle. Various adaptations, however, sooner or later appear, and these have been more fully considered by Mitchell.[41] Possibly, in the presence of undernutrition, the anterior portion of the pituitary body reduces its excretion of the growth hormone and thus lessens the need for protein by slowing the speed of growth. Other glands may then be affected, and osseous development and the genital changes associated with pubescence may be delayed. There is some evidence that these results actually do occur.

A number of classic studies in the literature show the effect of differences in dietary habits of different tribes on growth and health. The predominant differences in the diets of these physically different tribes were in the quantities of milk, meat and other animal foods consumed. Hence, the major, if not the principal, variants in them would be in the quality and quantity of the protein provided. The studies of Orr and Gilks[15] referred to above offer a striking example. Two South African tribes living side by side under the same climate and with the same agricultural possibilities were chosen for study because they differed strikingly in size and vigor. The larger and more vigorous was a pastoral tribe and lived mainly on milk, meat and freshly drawn blood, whereas the smaller and less vigorous subsisted for the most part on cereals, roots and legumes. The children of the latter tribe were not only smaller than those of the former but were also much more subject to skeletal and dental defects and generally more poorly developed.

The studies of McCarrison[42] on three tribes in India dealt with one tribe characterized by magnificent physique, unusual fertility and long life, and with two contrasting tribes in these respects. The superior tribe customarily took a simple diet of natural foodstuffs high in all the dietary essentials, the other tribes taking diets low in many of the essentials and obtained largely from plant sources. McCarrison's[43] findings on animals fed the same diets were even more striking. It is interesting that Mullick[44] recently repeated in India McCarrison's classic experiment on rats, with essentially the same results.

The well recognized fact that children of foreign nationals, such as the Japanese, born and brought up in this country are larger than their cousins who continue to live in their country of origin is further evidence along this line, in view of the associated differences in their diets under the changed circumstances.

The many studies of this type are in general agreement that, although heredity plays an important part, other influences are operative in determining racial and national differences in physique and that diet probably plays a definite part. The principal dietary difference as related to growth and development in childhood seems to be in the consumption of milk and other animal foods, and hence in the quality and quantity of protein. The evidence is quite striking that this characteristic of diet is a major factor in determining the degree of muscular development and the general level of physical robustness, energy and health of a people.

The literature dealing with diet supplements in relation to growth and health during childhood appears to be contradictory and confusing. Kruse[45] has considered the factors involved that make this understandable and has presented a comprehensive bibliography. Obviously, when the diets of a group of children are adequate to provide for all needs, benefits will not be demonstrable from supplements, and the effect obtained in a given case will depend on the general level of deficiency in the basal diets of the groups studied. On the other hand, when diets are grossly and generally inadequate, almost any supplement will usually show some results.

Of the many studies of this sort, applied principally to school children, the classic experiment of Mann[46] in England is still outstanding. Two hundred boys six to ten years of age were studied over a four-year period. The children given a pint of milk daily in addition to the basic diet, which was taken by them and by the control group and which contained some milk, gained in weight and height considerably more than the children not given the milk supplement. They were also considered to be markedly improved in general fitness and in health. Subsequently, a number of well controlled studies led to substantially the same results.

The characteristic changes in the diets of large populations of children in Europe due to famine conditions associated with the recent war have been a general lowering of food intake, without characteristic or special lack of any one specific essential. This is in sharp contrast to the changes during World War I, because of increased knowledge of nutrition and better planning and rationing. A sharp increase in the incidence and severity of rickets in childhood was a principal effect of World War I in Europe, but this was not a prominent result of the later war. The major inadequacies in the diets of children have been in total calories and total protein and in the percentage of protein from animal sources. This combination of deficiencies is well suited to bring out the effects of protein inadequacy on growth, but it does not lead to many cases of specific deficiency diseases. The effects on growth have been said to be hard to recognize because they are insidious and cannot be measured without careful observations before and following the periods of food shortages. The customary brief sampling survey usually fails to detect them or at least to measure them.

I spent some time during World War II attempting to collect evidence on these effects in studies of children in France, where, as elsewhere, a primary difficulty was lack of precise prewar standards with which to compare war and postwar children. Certain differences found in 1941 between French and American children[47] may well have resulted from this type of dietary, but it could not be said at the time that they were not national characteristics. After following a small group of the same children in Marseilles over a period of two or three years, Kuhlmann[48] found that as a group they failed to progress in weight and height to the amount expected for age. Although the numbers successfully followed were too small to give these results convincing significance, in approximately half the children studied growth was moderately but definitely retarded on the basis of normal expectancy and the average increment was approximately two thirds of expectancy.

Osseous development cannot be measured with sufficient precision to determine whether, in a given year or two, a group of children have fallen behind to a measurable degree, but it is of interest that in children studied in France in 1942 osseous development was, on an age basis, retarded in comparison with American standards to approximately the same relative extent as body size.[49]

Another striking characteristic of the children in France and other countries suffering from war restrictions has been their lassitude and inactivity. This physical inactivity tends to spare calories and may conserve protein for structural purposes and appears to be another manifestation of natural adaptation. Diminished activity in childhood causes failure of normal muscle growth, complete inactivity leading to rapid muscle atrophy. It may be said with reasonable certainty that one of the major characteristics of chronic undernutrition in childhood is poor muscular development, and this has been one of the most striking features of the children seen in war-devastated or famine countries. This poor growth of muscle may be attributed to the lack of sufficient protein in the presence of inadequate calories or to lack of activity or, as seems likeliest, to a combination of these.

Keys,[50] in controlled experiments on conscientious objectors during the recent war, provided diets typical of those in the countries severely affected by the war. He found that most of the weight loss occurring during semi-starvation was due to the loss of muscle tissue. Other striking physical effects were progressive weakness and fatigue. In examining children in France I was impressed with the number who had reasonable amounts of subcutaneous tissue and hence appeared superficially to be well nourished and yet had extremely small and flabby muscles. This suggests that with loss of weight there is some initial loss of subcutaneous fat, but that after this has progressed to a certain but variable degree, further loss is primarily in muscle. The children with poorly developed muscles were frequently found also to have rather spindly bones, and both linear growth of bones and osseous development appeared to be retarded. Owing to a lack of suitable prewar norms for comparison, however, this cannot definitely be stated to be a result of war. The question of an associated calcium factor enters into the picture. Protein and calcium are both liberally used in the construction of new bone. McCance[51] has shown that calcium absorption is far more satisfactory when a high-protein diet is taken than when protein intake is low. Although the children in France received little milk and rarely any vitamin D supplement, clear evidence of rickets or poor calcium deposition in the skeleton was rarely seen after infancy, but the bones of these children frequently showed lines of interrupted growth. It may be that the poor bone growth observed in France was in part due to unsatisfactory amounts of vitamin D and calcium. It is probable, however, that it was also due to some extent to lack of protein, aggravated by the inadequate provision of calories.

Each of these studies may be considered a piece in a picture puzzle that is as yet far from complete. The general outline that is beginning to emerge, however, reveals that poor growth and development — particularly faulty muscle development and general lack of physical fitness — are frequent consequences of chronic low-calorie, low-protein nutrition in childhood.

I am greatly indebted to Mrs. Bertha S. Burke for assistance in the preparation of this review.

References

35. Levine, S. Z. Protein nutrition in pediatrics. *J. A. M. A.* **128**:283-287, 1945.
36. Hegsted, D. M. Minimum protein requirements of normal adults. Lecture given in Symposium on Body Protein, University of Buffalo, September, 1946. (To be published in University Centenary volume.)
37. Talbot, N. B., Sobel, E. H., Burke, B. S., Lindemann, E., and Kaufman, S. B. Dwarfism in healthy children: its possible relation to emotional, nutritional and endocrine disturbances. *New Eng. J. Med.* (in press).
38. Leitch, I., and Duckworth, J. Determination of protein requirements of man. *Nutrition Abstr. & Rev.* **7**:257-267, 1937.
39. Youmans, J. B. *Nutritional Deficiencies: Diagnosis and treatment.* Second edition. 389 pp. Philadelphia: J. B. Lippincott Co., 1943.
40. *Idem.* Nutrition and war. *New Eng. J. Med.* **234**:773-783, 1946.
41. Mitchell, H. H. Adaptation to undernutrition. *J. Am. Dietet. A.* **20**: 511-515, 1944.
42. McCarrison, R. Faulty food in relation to gastro-intestinal disorder. *J. A. M. A.* **78**:1-8, 1922.
43. *Idem.* Problems of nutrition in India. *Nutrition Abstr. & Rev.* **2**:1-8, 1932.
44. Mullick, D. N. Investigations into Indian diets. I. Their effect on health and well-being of three generations of rats. *Ann. Biochem. & Exper. Med.* **2**:25-32, 1942.
45. Kruse, H. D., Besser, O. A., Jolliffe, N., McLester, J. S., Tisdall, F. F., Wilder, R. M., and Sydenstricker, V. P. W. Principles underlying studies of nutrition pertaining to influence of supplements on growth, physical fitness and health with comprehensive bibliography of studies: report by Committee on Diagnosis and Pathology of Nutritional Deficiencies, National Research Council. *Arch. Int. Med.* **74**:258-279, 1944.
46. Mann, H. C. C. *Diets for Boys during the School Age.* 81 pp. Medical Research Council, Special Report Series No. 105. London: His Majesty's Stationery Office, 1926.
47. Stuart, H. C., and Kuhlmann, D. Studies of physical characteristics of children in Marseilles, France, in 1941. *J. Pediat.* **20**:424-453, 1942.
48. Kuhlmann, D. Personal communication.
49. Stuart, H. C. Studies of nutritional state of children in unoccupied France in fall of 1942: preliminary report. *J. Pediat.* **25**:257-264, 1944.
50. Keys, A. Human starvation and its consequences. *J. Am. Dietet. A.* **22**:582-587, 1946.
51. McCance, R. A., Widdowson, E. M., and Lehmann, H. Effect of protein intake on absorption of calcium and magnesium. *Biochem. J.* **36**:686-691, 1942.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 33151

PRESENTATION OF CASE

First admission. A forty-five-year-old Lithuanian leather tanner entered the hospital complaining of a chronic cough and blood-streaked sputum.

For about six months before admission the patient had had a slight, chronic cough productive of a small amount of white sputum, especially in the morning. Five weeks before entry the cough began to increase, and streaks of rust-colored blood began to appear in the sputum. There was no pain, fever, weakness, sweating or dyspnea. In the two years before admission the weight had risen from 170 to 200 pounds.

For many years recurrent bouts of "tonsillitis" had caused occasional severe sore throat. The last of these had occurred a year and a half before admission, at which time the tonsil "broke," discharging blood and pus.

On admission the only abnormal physical findings were generalized rhonchi that decreased after coughing and expectoration. An x-ray film demonstrated a round area of consolidation in the posterior aspect of the right upper lobe adjacent to the septum, measuring about 5 cm. in the transverse diameter. The right middle lobe was collapsed. On the second day the temperature was 100°F., but afterwards it remained between 98 and 99°F. The white-cell count was 12,000, with 76 per cent neutrophils.

At bronchoscopy the posterior wall of the right main bronchus was displaced forward by extrinsic pressure. The upper-lobe orifice was in the center of the area of extrinsic pressure. Blood oozed from the upper-lobe bronchus, and the middle orifice was reddened. No tubercle bacilli were found in the sputum. A bougie passed into the middle-lobe bronchus without difficulty. The lower bronchi were normal. At the end of a week the patient was discharged to be followed in the Out Patient Department.

Final admission (six years later). In the four months following discharge the patient was seen several times with no change in his status. He failed to keep succeeding appointments and was not seen until six years later, when he was referred from another hospital because of fluid in the right side of the chest. He claimed to have been free of symptoms, except for two brief episodes of coughing blood-streaked sputum. These occurred, respectively, four years and one year before readmission, and each lasted about a day. Six weeks before admission a mild productive cough had developed in association with intermittent rusty streaking of the sputum. Four weeks later the patient became feverish, had a headache and felt chilly, although he experienced no frank chill. At the other hospital x-ray studies showed "a right hydrothorax rising to the fifth rib posteriorly." Ten to 15 cc. of brownish fluid was removed at each of several thoracenteses. Penicillin and sulfadiazine were given with no effect on the temperature, which remained elevated. After two weeks, the patient was transferred to the Massachusetts General Hospital.

Physical examination disclosed an obese, pale, sweating and feverish patient. The right side of the chest up to the apex was completely flat to percussion. Bronchial breath sounds were audible over the right upper lobe. Breath sounds and tactile fremitus were "negative" over the lower lobe and depressed over the middle. The left lung was normal. Abdominal, rectal and neurologic examinations revealed no significant abnormalities.

The temperature was 103°F., the pulse 90, and the respirations 25. The blood pressure was 114 systolic, 64 diastolic.

Examination of the blood showed a red-cell count of 4,400,000, with a hemoglobin of 11 gm. per 100 cc., and a white-cell count of 8120, with 67 per cent neutrophils. The urine, blood sugar, total protein and nonprotein nitrogen were normal. On x-ray examination the right lung appeared dense, with the exception of a small aerated area in the upper right portion of the chest. The heart and mediastinum were markedly displaced to the right. The left lung was clear.

In the hospital the temperature spiked from 103 to 104°F. every day. Abundant colonies of alpha-hemolytic streptococci grew from the sputum. Penicillin was started, with no effect on the fever. An operation was performed on the tenth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. RALPH ADAMS*: May we see the x-ray films?

DR. RICHARD SCHATZKI: All the films that were taken are not here; there are no films from the first admission. This film shows the mediastinum displaced to the right and air in the apex of the right lung.

DR. ADAMS: Do you consider this area of density to be bony in character?

DR. SCHATZKI: It looks like it.

DR. ADAMS: Also, on the film the manubrium is outlined, and the trachea is displaced to the right. One can postulate a shadow in this region of the tracheal bifurcation that was not mentioned in the record. Is that actually something, or is it again an artefact?

*Surgeon, Lahey Clinic.

DR. SCHATZKI: This is not an artefact. It may be the edge of the left lung, but it seems to be far over.

DR. ADAMS: The edge seems to be clearly outlined.

DR. SCHATZKI: Anteriorly, and I suppose that this is the posterior edge of the lung.

DR. ADAMS: A final question: Is the apparent defect in the ribs overlying air in the lung rather than disease in the bone?

DR. SCHATZKI: I would say that it is not a defect in the rib.

DR. ADAMS: The history for six and a half years with a proved mediastinal shift indicates a chronic intrathoracic disease. As stated in the record, symptoms typical of bronchial irritation were present at the onset. Six weeks before the final admission the patient developed signs of bronchial invasion or ulceration as reflected by the increase in the cough and the appearance of rust-colored sputum. These symptoms were not obstructive in character, since there was absence of pain or fever, and the process was not causing inflammation or irritation of the pleural surface or interfering with respiratory function. Pain in lung disease practically always comes from irritation at some point of either the visceral or the parietal pleura. The gain of 30 pounds in weight in two years is almost exclusive of carcinoma, in spite of the classic symptoms of initial slight cough with mucoid sputum, later increasing and accompanied by blood. The recurrent bouts of "tonsillitis" seem to be irrelevant to this problem unless one of those episodes had caused a lung abscess. The subsequent course after the last episode is inconsistent with the supposition of lung abscess. He did not have symptoms for the ensuing year, and when the symptoms appeared, he was afebrile and the sputum was neither foul nor purulent.

The initial physical examination is not helpful except that it excludes the presence of marked bronchial obstruction at that time. The description of the x-ray findings at the first admission mentions an area of consolidation. Whether this abnormality was a mass or an area of pneumonitis, it is impossible to say without seeing the films, which are not available. Also, the consolidated area is described as adjacent to the septum. It might be of importance to know which septum, the major or the minor, but again the information is not at hand. It is impossible to account for collapse of the right middle lobe by a lesion in the posterior part of the right upper lobe, except by extrinsic pressure from a mass that would have to arise in the region of the lateral segmental bronchus of the right upper lobe. Presumably, as shown by the slightly elevated temperature and slight leukocytosis, there was some associated pneumonitis with mild obstruction at that time. It was the posterior wall of the right main bronchus that was displaced forward by extrinsic pressure. The posterior wall is the membranous or yielding portion of the bronchus. The upper-lobe orifice is described as being in the center of the area of extrinsic pressure. There was a pathologic process in or invading the upper lobe as proved by blood oozing from the upper-lobe bronchus, and this is the first proof that the hemoptysis was coming from the same region as that in which the mass seemed to be localized. The statement that no tubercle bacilli were found in the sputum is assumed to mean that adequate bacteriologic examination of the sputum was done really to exclude that diagnosis, and we will henceforth leave tuberculosis out of consideration. The passage of a bougie into the middle-lobe bronchus without difficulty demonstrates that the right middle lobe was collapsed by extrinsic pressure rather than by an intrinsic mass.

The patient was discharged without a histologic diagnosis but with the following evidence as a matter of record: he harbored a mass originating in, invading or ulcerating into the lateral bronchus of the right upper lobe, pressing on the posterior wall of the right primary bronchus and causing collapse by extrinsic pressure of the lower lobe. The surgical service did not know the man's trouble, did not think he needed surgical treatment, or were afraid to offer it, or the patient refused to accept it. That there was no lack of confidence is attested by the patient's continued visits to the Out Patient Department. That he was unimpressed by the potentialities in his case is suggested by the failure to keep appointments after four months and his claim of freedom from symptoms for the next six years — he was free of symptoms, that is, except for two episodes of coughing blood-streaked sputum, which were widely separated by intervals of four years and one year previous to the second admission. On readmission, he had symptoms and signs denoting enlargement of the mass to sufficient size to cause obstruction of the bronchi and pulmonary suppuration in the right lung; yet bleeding was minimal, sporadic and not daily as in carcinomatous ulceration.

The physical findings are not helpful. One word is puzzling in the sentence in which it is stated that the breath sounds and tactile fremitus were "negative." Tactile fremitus is present or absent, increased or decreased, but how it is "negative," I do not know. Dr. Mallory kindly showed me a diagram found in the record of the physical findings, which were, in brief, those of an obstructed lung. The other hospital's interpretation of fluid extending to the fifth posterior rib is altered by reading of the heavy-exposure film taken at the Massachusetts General Hospital to an interpretation of obstructive atelectasis of the right lung, and that interpretation seems to be supported by the clinical chart, the high temperature and the signs of infection. There was a secondary anemia consistent with the status of the illness and infection. Penicillin was given with no more effect on the fever than might be anticipated with bronchial obstruction present.

The question, then, is resolved into the nature of this tumor mass in a fifty-one-year-old Lithuanian

leather tanner — a tumor that started like carcinoma, grew like adenoma and looked like a dermoid. The duration of the manifestations of disease, the long periods of freedom from complaint, the gain in weight and the absence of demonstrable metastases lead one to exclude carcinoma from further consideration in the differential diagnosis. If carcinoma was present in this case, it was only as a degenerative end product in a tumor with a different beginning. If the age and sex of the patient are excluded, this case report is a classic description of bronchial adenoma. Patients with such tumors usually have had symptoms of cough and sporadic hemoptysis for many months when first seen by thoracic consultants. They are in general in good health. The x-ray examination shows signs of bronchial obstruction. In a number of years, even if intraluminal tumors are cleared away, bronchoscopically, extraluminal growth may cause extrinsic pressure leading to obstruction and suppuration and, finally, to resection. Most cases occur in women. Seven out of 8 occur in women under forty years of age. This should be compared with carcinoma, in which 3 out of 4 cases occur in men and in which 5 out of 7 are in patients over forty years of age. The incidence of adenoma is 5 to 10 per cent of that of carcinoma, and five-year cures are obtained in 95 to 100 per cent of cases. The five-year curability rate for resectable carcinoma of the lung is around 7 per cent. Other noncarcinomatous tumors of the lung, such as a hamartoma, myxochondroma and sarcoma, have been seen as solitary examples but have shown no similarity helpful to the differential diagnosis in this case. The lateral and posterior displacement of the trachea, the localized calcification of bony density resembling a canine tooth and the area of surrounding rarefaction, instead of solid density that is expected from a solid tumor, cause one to postulate the presence of a dermoid cyst with rupture into the bronchus as the cause of this man's difficulty and the source of the brownish fluid obtained in quantities of 10 to 15 cc. at the other hospital on several occasions. The expectoration of hair or the like, debris, fluid or sputum containing cholesterol crystals or fat droplets, however, was not described in the record. Therefore, I shall have to follow the statistical-likelihood precept of the clinician for whom these exercises are named and make a diagnosis of obstructive bronchiectasis of the right lung caused by bronchial adenoma.

Dr. Donald S. King: Dr. Adams, I think that our bad pennies have returned. This is a case that you and I saw in 1940. Dr. Schatzki also saw the x-ray films in 1940. I will read the three notes made at that time. Dr. Schatzki says, after describing the x-ray films, "I do not believe that this is an abscess. The localized area of collapse in the upper lobe is most probably due to bronchiogenic tumor. This is the likeliest diagnosis."

My note reads, "Diagnosis not yet clear. No definite evidence of tumor. There may have been two pulmonary infarcts, one in July and one in August. Would like to see the patient in the Pulmonary Clinic in four weeks."

You saw him in the Pulmonary Clinic, Dr. Adams, and wrote, "Patient continues in good health. Only complaint is blood-streaked, brown sputum about every third morning — small amount, not foul. Believe episodes are decreasing. No pain in chest, no loss of weight or appetite. Patient advised and reassured. To return for a repeat x-ray film."

The patient himself wrote, "I cannot make the appointment to have the x-ray film repeated. Have a bad cold. Will be in when my cold is better." That is the last that was heard from him.

I saw him when he came back last fall, and our diagnosis was the same as yours — an adenoma of the bronchus.

Dr. Carroll B. Miller: The transcribed history stops at the second bronchoscopy. I am sorry that Dr. Benedict is not here to describe the operation. He had a trying time with the patient. He found a spongy, easily bleeding mass, which he biopsied. The patient was difficult to handle at that point. A good deal of blood and tumor was aspirated over into the left bronchus. Dr. Benedict had enough of a view of the carina and the two bronchi to tell fairly well that this was a tumor mass that had almost completely obstructed the right main bronchus. The preliminary pathological report of the biopsy was carcinoma. The patient was referred for exploration. We fully expected the tumor to be inoperable because of the diagnosis of carcinoma returned by the Pathology Department and because of the time interval between the first admission and the last; when we opened the chest, however, we found that the upper lobe was completely collapsed, as we expected, and the middle and lower lobes moderately collapsed, but there was no fluid in the chest and, curiously enough, the mass surrounding the upper-lobe bronchus was small. It was decided because of the location that it would be necessary to do a pneumonectomy. I cut across the main bronchus and found in my incision in the bronchus a tongue of tumor extending 3 mm. beyond the point of incision. I was able to extend the incision and get completely around the tumor and do a pneumonectomy, with division of the right bronchus. On inspecting the specimen afterward, we found that the attachment of this tumor, so far as the bronchus was concerned, was several millimeters distal to my incision, with a thumblike projection extending up into the bronchus.

Clinical Diagnosis

Carcinoma of bronchus?
Adenoma, right-stem bronchus?

Dr. Adams's Diagnosis

Bronchial adenoma, with obstructive bronchiectasis.

Anatomical Diagnosis

Basal-cell papilloma of bronchus, with cornification.

Pathological Discussion

Dr. Tracy B. Mallory: The bronchoscopic biopsy from this patient gave the laboratory a difficult problem because it was unlike any bronchiogenic tumor we had ever seen or, so far as I know, any that has heretofore been reported. It was obviously epithelial and contained foci of squamous cells and yet did not look like a squamous-cell carcinoma. After struggling several days with it, we finally returned a diagnosis of basal-cell carcinoma with foci of cornification. Our hesitation was largely based on our belief that so-called "basal-cell carcinomas" are actually tumors of the skin

Figure 1.

appendages and, therefore, should not occur in mucous membranes. In the registry of lung tumors, however, I have seen a case that was indistinguishable from a basal-cell carcinoma of the skin.

When the lung was resected a large endobronchial tumor was found that had spread through the branches of the upper-lobe bronchus (Fig. 1). It was attached to the bronchial wall at one point only and elsewhere could be readily shelled out with the gentlest of blunt dissection. We could make out no invasion of the lung tissue.

In the group of bronchial adenomas reported from the Army Institute of Pathology by Holley* the tumors are classified into two types, the usual form, which strongly resembles a carcinoid of the appendix, and a second glandular or pseudoglandular type, which sometimes resembles closely the tumors of the salivary glands that have been described as cylindromas. None of Holley's cases, however, resembled the tumor in the case under discussion, in which the majority of the cells were small, basophilic and slightly spindle shaped (Fig. 2).

Figure 2.

They were oriented at right angles to the stroma. Occasional cells showed various degrees of cornification. The appearances slightly suggested adamantinoma, and one pathologist who saw the sections was willing to make this diagnosis. I finally called the tumor a basal-cell papilloma with cornification. The regional lymph nodes were free from metastasis, and I believe that the prognosis is good.

*Holley, S. W. Bronchial adenomas. *Mil. Surgeon* 99:528-554, 1946.

CASE 33152

Presentation of Case

A forty-three-year-old Italian baker entered the hospital because of jaundice.

Eight weeks before entry the patient had begun to have epigastric discomfort after meals, particularly if the food was fatty or fried. He also complained of fatigue, anorexia and "a heavy head" but continued to work at his job. Six weeks before entry he began to have postprandial nausea. On three occasions he vomited about thirty minutes after

eating. Three weeks before entry, while returning from work at 3:00 a.m., he was seized with a severe, colicky, right subcostal pain that occurred in spasms lasting five to ten minutes at a time. For the next five hours he had many such spasms associated with restlessness, sweating, chills, weakness and nausea. He also had occasional stabs of knifelike pain beneath the left scapula. That evening his wife noticed that the eyes were yellow. During the next few days he rapidly developed generalized jaundice and itching severe enough to keep him awake at times. The urine became dark colored and the stools clay colored. Passage of the dark urine was associated with burning. The patient also became constipated, moving the bowels only every two to four days. Two weeks before entry these symptoms had progressed to the point where the patient had to stop working. He saw a physician, who prescribed "pills," bed rest and a fat-free diet. Five days before entry he began to have chilly sensations, alternating with sensations of warmth. He had had no more attacks of colic, but there was some residual soreness in the right upper quadrant. He had lost 15 pounds during the two weeks before entry.

The patient's health had previously been excellent except for mild exertional dyspnea and some ankle swelling after long hours on his feet.

Physical examination revealed an intensely jaundiced, moderately obese man showing multiple scratch marks of the skin. The heart and lungs were normal. The liver was firm, smooth and moderately tender. Its margin was palpated 7 cm. below the costal margin in the midclavicular line. The spleen was not palpable.

The temperature was 98°F., the pulse 60, and the respirations 20. The blood pressure was 140 systolic, 100 diastolic.

Examination of the blood disclosed a red-cell count of 5,280,000, with 12.0 gm. of hemoglobin, and a white-cell count of 13,000, with 78 per cent neutrophils. The serum phosphorus was 4.4 mg., the nonprotein nitrogen 31 mg., the total protein 7.7 gm., the cholesterol 312 mg., and the cholesterol esters 158 mg. per 100 cc., and the alkaline phosphatase 3.8 units and the amylase 12 units per 100 cc. The van den Bergh reaction was 14.4 mg. per 100 cc. direct, and 19.0 mg. total, and a cephalin-flocculation test was negative after twenty-four hours and + after forty-eight hours. The prothrombin time was normal.

The urine gave a + test for albumin and a ++++ test for bile. Urobilinogen was present in a dilution of 1:8. The stools were slightly yellow and gave a positive guaiac test. Examination of the sediment from duodenal drainage showed absence of bile; the sediment contained numerous red cells and white cells. A gastrointestinal series showed a constant deformity of the duodenal cap, in the center of which was an ulcer crater. The esophagus, stomach and lower portions of the duodenum were normal. Sigmoidoscopy was negative.

The patient was placed on hykinone, atropine and a high-protein, high-carbohydrate, high-vitamin diet.

On the eleventh hospital day an operation was performed.

Differential Diagnosis

Dr. Leland S. McKittrick: Before seeing the x-ray films, let us summarize the story. The patient stated that eight weeks before admission he had had epigastric discomfort, with some malaise and nausea, and that five weeks later he had had attacks of colicky right-upper-quadrant pain — the pains were apparently colicky because they came in spasms, lasting from five to ten minutes. He then began to be restless, had chills and some nausea, and developed jaundice. Physical examination on entry did not reveal much, except a liver that was slightly low and moderately tender, and x-ray films showed a presumable duodenal ulcer.

Dr. Richard Schatzki: The films show a definite clover-like deformity of the duodenal cap. There is evidence of long-standing duodenal ulcer and probably a crater in the area of maximal constriction. I cannot see any abnormality in the second portion of the duodenum.

Dr. Arthur W. Allen: How large a crater is that?

Dr. Schatzki: I am not sure, as a matter of fact, but I should say about 4 mm.

Dr. McKittrick: I cannot put this history together and make it add up to any clear-cut diagnosis. Perhaps the thing to do is to take an outstanding symptom, which is jaundice, and see if we can reason from that and get somewhere. Was this jaundice, which was obviously not the hemolytic type, due to intrahepatic disease or to obstruction of the external biliary tract?

The patient had pain, but the pain was not sufficiently distinctive to mean much to me. The jaundice is somewhat confusing — it was apparently complete. At least, the patient had clay-colored stools on admission, and there was no bile in the duodenal contents; I take that statement as being evidence of complete jaundice. The liver was slightly enlarged and moderately tender, but that again does not give us too much help. The spleen could not be palpated. If it had been palpable, I think that we could take that as evidence of a process within the liver, but it could not be felt so that we get no help from that. No mention is made of a palpable gall bladder — evidence that would permit the assumption that the process was in the extrabiliary tree.

The laboratory evidence is slightly confusing. I do not know just how frequently a normal alkaline phosphatase is found with obstructive jaundice. Certainly an alkaline phosphatase of 15 units or

more favors an obstructive type of jaundice. I would suppose that by that time the phosphatase would have been elevated if it followed the usual rule in obstructive jaundice. The cholesterol was slightly elevated. The serum amylase was normal, and the bilirubin was elevated, as might have been anticipated with complete jaundice of that duration. Thus far, the onset of jaundice after atypical transient right-upper-quadrant pain, with absence of a palpable gall bladder, and the low alkaline phosphatase favor jaundice of intrahepatic origin. On the other hand, the normal prothrombin time, the negative cephalin-flocculation test and the absence of a palpable spleen may be taken as evidence against the jaundice being due to liver damage.

I am disturbed about the symptoms five or six weeks before the patient became jaundiced. It seems to me — and this is not on the basis of experience really — that five weeks of prodromal symptoms before developing jaundice is rather longer than I should have anticipated with an acute hepatitis. Thus, I am still unable to reach any definite conclusions but am nevertheless forced to try to make a diagnosis that I am perfectly sure is not going to be correct.

I believe that this patient did not have primarily intrahepatic disease; the evidence is more against than in favor of that diagnosis. I do not believe that the symptoms were due to gallstones. It is unusual for a patient of forty-three, with complaints of only eight weeks' duration, to have a history suggestive of gallstones so indefinite as this, beginning with slight epigastric distress and itching and going into a period of fatigue, malaise and "a heavy head" and then nausea and vomiting. That is so unlike uncomplicated gallstones that it would be impossible for me to feel confident about making such a diagnosis in this man.

The patient had a duodenal ulcer. I cannot get away from the fact that this lesion was probably in the duodenum, and again I cannot state definitely why I get that impression. It is probably because I do not believe that he had intrahepatic disease or gallstones. I had hoped that Dr. Schatzki would show a large crater or something else and that there had been reaction enough around the ulcer to make it possible for jaundice to have been secondary to that.

Carcinoma of the ampulla of Vater, of course, is perfectly possible, but I cannot make this diagnosis, nor can I exclude it.

I must leave this case without a satisfactory diagnosis in my own mind and simply say that the patient had an ulcerating lesion in the duodenum, which in some way was responsible for obstruction to the common duct.

Dr. Tracy B. Mallory: Are there any suggestions or comments? Dr. Giddings, would you give the opinion on the ward?

Dr. W. Philip Giddings: We thought definitely that this man had complete obstructive jaundice, as Dr. McKittrick has deduced. We also were rather puzzled regarding the pain and the exact nature of the obstruction. The patient had two conditions — complete obstructive jaundice and blood in the stools — that we tried to add up to a carcinoma of the ampulla. He gave a definite history of pain. There was no palpable gall bladder, however, and there was x-ray evidence of an active duodenal ulcer.

Dr. Mallory: Will you give the operative findings?

Dr. Giddings: We operated with a diagnosis of two diseases: common-duct stone and duodenal ulcer. It was quite apparent that the patient did not have gall-bladder disease. The gall bladder was completely normal, but the common duct was greatly dilated — about the size of a man's thumb. At the lower end of it was a readily palpable tumor. The duct was opened and found to contain crystal-clear white bile, and we could visualize within it a tumor mass that had the appearance of carcinoma. This was biopsied, and adenocarcinoma reported. We did a two-stage Whipple procedure, at the first operation transecting the common duct as high as we could beneath the hepatic artery, and performing a routine type of anastomosis. About three weeks later, after recovery from the jaundice, we completed the Whipple type of resection, including the head of the pancreas and the duodenum.

Clinical Diagnoses

Common-duct stone.
Duodenal ulcer.

Dr. McKittrick's Diagnosis

Ulcerating lesion of duodenum, with secondary obstruction of common duct.

Anatomical Diagnosis

Carcinoma of common bile duct.

Pathological Discussion

Dr. Mallory: The specimen that we were finally provided with consisted of the pyloric end of the stomach, a major part of the duodenum, a segment of the common bile duct and a segment of the head of the pancreas. In the common bile duct slightly posterior to the papilla was a primary carcinoma that had extended into the surrounding tissues. We were completely unable to find any trace of duodenal ulcer. I have no explanation for the discrepancy.

Dr. Schatzki: Was anyone from the X-Ray Department present?

Dr. Mallory: I cannot answer that.

Dr. Schatzki: The reason I ask is that we have seen cases in which ulcers have entirely disappeared between the time of examination and either operation or autopsy; I think it is inconceivable that there was no ulcer at the time of examination, although it may have healed by the time of resection.

The New England
Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Owned by the Massachusetts Medical Society and Published under the Jurisdiction of the Committee on Publications

Richard M. Smith, M.D., *Chairman*
James P. O'Hare, M.D. Conrad Wesselhoeft, M.D.
Oliver Cope, M.D. John Fallon, M.D.

Official Organ of
The Massachusetts Medical Society
and
The New Hampshire Medical Society

Editorial Board

Joseph Garland, M.D. Chester M. Jones, M.D.
Shields Warren, M.D. Harvey R. Morrison, M.D.
C. Guy Lane, M.D. Maxwell Finland, M.D.
Henry R. Viets, M.D. James M. Faulkner, M.D.
Robert M. Green, M.D. Carroll B. Larson, M.D.
Chester S. Keefer, M.D. Francis D. Moore, M.D.
Fletcher H. Colby, M.D. C. Stuart Welch, M.D.
Robert L. Goodale, M.D. Vernon P. Williams, M.D.

Associate Editors

Thomas H. Lanman, M.D. Donald Munro, M.D.
Henry Jackson, Jr., M.D.

Walter P. Bowers, M.D., Editor Emeritus
Robert N. Nye, M.D., Managing Editor

Assistant Editors

Clara D. Davies Robert O'Leary

Subscription Terms: $6.00 per year in advance, postage paid, for the United States (medical students, $3.50 per year); Canada, $7.00 per year (Boston funds); $8.50 per year for all foreign countries belonging to the Postal Union.

Material should be received not later than noon on Thursday, two weeks before date of publication.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts.

CURARE

There is something spectacular about the introduction of a new drug that immediately achieves for itself a wide field of usefulness. Only slightly less spectacular is the discovery of a new and widespread use for an old drug; to this category belongs curare.

Curare, the ancient arrow poison of certain South American Indians, has been known for over three hundred years. Sir Walter Raleigh is credited with being the first White man to observe its effects. He apparently became acquainted with it during his famous voyage up the Orinoco in 1595. The ability of curare to effect muscular relaxation and loss of tone by paralysis of the myoneural junction has been known for many years. In fact, no less a person than Claude Bernard established this fact experimentally and suggested the therapeutic use of curare in hydrophobia, chorea, tetanus and epilepsy. For many years after his investigations, curare remained essentially a pharmacologic curiosity and a physiologist's tool for the demonstration of the existence of the myoneural junction as a physiologic entity.

To Mr. Richard C. Gill must go the credit for many modern conceptions concerning this drug. Mr. Gill spent a great deal of time in the Amazonian jungles, and it was he who first brought to this country, in 1938, adequate supplies of the drug for accurate assays and standardization. He[1] has recently pointed out that curare is not derived from a single species of plant but is a mixture of botanical components widely distributed throughout both North and South America, more particularly in the region around the Amazon River. McIntyre[2] and Bennett,[3] of the University of Nebraska, were the first to investigate modern curare pharmacologically and to submit it to clinical trial.

Following the investigations of McIntyre and Bennett, curare was first used in the field of psychiatry in an attempt to overcome some of the less desirable side effects of convulsive shock therapy in the treatment of various psychoses. Since the forceful muscle contractions associated with this type of therapy not infrequently resulted in fractures and muscle rupture, it was desirable to have some method of lessening their severity.

Griffith and Johnson,[4] of Montreal, introduced this drug into the field of anesthesiology in 1942. Their initial report of its use in twenty-five surgical operations was extremely promising. Since that time, many workers in laboratories and clinics have reported favorably on the benefits to be derived by a combination of a general anesthetic, to render the patient insensible to pain, and the intravenous injection of curare, to provide muscular relaxation.

Recent work in the laboratory with this drug has confirmed the statement of Claude Bernard that the primary action was at the myoneural junction. With adequate doses, curare so completely blocks the myoneural junction that the muscles no longer respond either to mechanical stimulation or to the injection of acetylcholine. Curare does not affect nerve conduction.

Curare is not an anesthetic agent or a hypnotic, although the administration of large doses is said

by some to result in unconsciousness. This drug produces in conscious patients progressive weakness of the eyelids and strabismus with diplopia, followed by weakness of the throat and jaw muscles and the muscles of the extremities and trunk. Overdosage causes complete respiratory paralysis. The last may be a terrifying experience, and the drug should therefore not be used except in combination with a general anesthetic.

In anesthetic practice, curare may be combined with any of the general anesthetic agents, such as nitrous oxide, ethylene and cyclopropane. If it is used with ether or Pentothal, both of which have a curariform action, the dose should be much smaller than when it is combined with the other agents.

If adequate respiratory exchange is maintained, this drug is apparently quite safe. The greatest danger lies in respiratory depression or even respiratory paralysis from overdosage. Curare should never be administered without adequate facilities for maintaining a patent airway and administering artificial respiration. It has been shown that it takes twenty times as much of this drug to kill dogs when artificial respiration is employed as when it is not. Curare is eliminated quite rapidly from the body. Most of it is broken down in the liver, and the remainder is excreted unchanged by the kidneys.

The pharmacologic antidote for curare is prostigmine. It must be remembered, however, that prostigmine must never be given in lieu of the establishment of a patent airway and the administration of artificial respiration, preferably with oxygen. If adequate respiratory exchange and a sufficient supply of oxygen are maintained, the use of prostigmine should never be necessary. Sufficient recovery of the muscles of respiration to carry on adequate respiratory exchange usually takes place within ten to fifteen minutes.

Abdominal relaxation under curare combined with a general anesthetic approaches that obtained with spinal anesthesia; most surgeons, however, believe that actual operating conditions in the abdomen may not be quite so satisfactory as those under spinal anesthesia. Contraction of the bowel, which is evident under spinal anesthesia, is not usually present when a combination of curare and a general anesthetic is employed.

This drug is unquestionably firmly established as an important addition to the already formidable group of anesthetic agents, and when used by anesthesiologists familiar with its advantages and yet acutely aware of its limitations, it can be a valuable aid to modern surgery. Observations regarding its use in two series of patients appear elsewhere in this issue of the *Journal*.

References

1. Gill, R. C. Curare: misconceptions regarding discovery and development of present form of drug. *Anesthesiology* 7:14-23, 1946.
2. McIntyre, A. R., and King, R. E. d-Tubocurarine chloride and choline esterase. *Science* 97:69, 1943.
3. Bennett, A. E. Preventing traumatic complications in convulsive shock therapy by curare. *J. A. M. A.* 114:322-324, 1940.
4. Griffith, H. R., and Johnson, G. E. Use of curare in general anesthesia. *Anesthesiology* 3:418-420, 1942.

THE INSTITUTE OF SOCIAL MEDICINE AT OXFORD

It is noteworthy that through the war-torn years in England plans were pursued for the development of an institution at Oxford University that has many potentialities for the betterment of social welfare. The Institute of Social Medicine came into being on April 1, 1943, when John A. Ryle was appointed the first professor of social medicine and subsequently director of the Institute.

By "social medicine" is meant neither schemes for socializing medicine nor medical social work; it is defined in the following stated purposes of the Institute:

> To investigate the influence of social, genetic, environmental and domestic factors on the incidence of human disease and disability.
>
> To seek and promote measures, other than those usually employed in the practice of remedial medicine, for the protection of the individual and of the community against such forces as interfere with the full development and maintenance of man's mental and physical capacity.
>
> If required by the University to do so, to make provision in the Institute for the instruction in social medicine of students and practitioners of medicine approved by the Board of the Faculty of Medicine in the University of Oxford.

Thus, the three principles of any great medical institution are incorporated in these purposes: research, medical care and the prevention of disease, and teaching.

The early years of the Institute have had to do with the organization of a number of worth-while projects. An investigation has been undertaken to study the development, health and sickness ex-

perience of a relatively large group of children up to the age of five. In collaboration with local factories, the Institute is investigating occupational morbidity to sickness and industrial hazards. A survey of how thyroid enlargement in school children is related to the iodine content of drinking water is being carried out extensively in several districts of England and Scotland. X-ray studies of growth and development of bone are being made. In connection with human genetic studies, a pilot survey of forty-two sets of twins of school age has been completed. Statistical analyses of stillbirth rates and neonatal death rates in certain counties and county boroughs are being made. Other activities have included problems in connection with confinement among women of the working class, health examinations, consultative work and the teaching of students in their clinical years at Radcliffe Infirmary. Perusal of the *First Annual Report*[1] suggests that the Institute is attempting to fill in the gaps left by governmental public-health methods of collecting and recording health statistics. Surely, if adequate methods of recording illnesses were put into practice, the work of statistical epidemiology would be much simpler than it is at present.

In his report, Professor Ryle speaks of "social pathology" in contrast to "human pathology," defining the former as follows: "The advancement of our knowledge of man in health and disease and . . . the investigation of the social causes of disease." Incorporated in the concept is the study of the healthy state and of the borderland involving disease. It is not difficult to realize that equal knowledge for human welfare will accrue from directing attention to factors having to do with healthy groups, as with those concerned with diseased groups, and that these are appropriately co-operative fields of investigation.

Elsewhere, Professor Ryle[2] has stated a point of view that deserves repeating again and again:

> We are most of us conscious of the fact that medicine during the past quarter of a century has become (inevitably, be it allowed) not merely more specialized but also more technical, and that in the process — for the technicalities are often precise, intricate and time-consuming — the old aetiological interest and humanism of our fathers have tended to take the second place. In the teaching hospitals this can scarcely be disputed. Investigation to the limit, mainly by objective methods and often with too little said to or done for the patient during or after the tedious process, has been the prevailing trend, especially in the case of the more chronic or seemingly more obscure varieties of disorder and disease. More and more accurate assessments of local pathology, with the help of more and more colleagues and instruments, and less and less intimate understanding of the patient as a whole man or woman with a home and anxieties and economic problems and a past and a future and a job to be held or lost, have become the order of the day. As we direct our students, so in large measure must the outlook and method of each new generation of doctors be determined.

Professor Ryle, who was formerly Regius Professor of Physic at Cambridge University, recently visited Boston, having given an address at the Harvard Medical School on February 24. His remarks centered about the need for a better understanding of normal variations. He sketched some of the methods that the Institute of Social Medicine is employing to attain this result. Those who met and heard Professor Ryle were deeply impressed. His undertaking deserves success, and it is suggested that his institution serve as a model for needed research activities in this country.

REFERENCES

1. *First Annual Report 1945*. 20 pp. Oxford, England: University Press 1945.
2. Ryle, J. A. Social medicine: its meaning and its scope. *Brit. M. J.* 2: 633-636, 1943.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

BIGELOW — Enos H. Bigelow, M.D., of Framingham, died March 13. He was in his ninety-second year.

Dr. Bigelow received his degree from Harvard Medical School in 1882. He was a former president of the Massachusetts Medical Society and a former chairman of the Framingham Board of Health.

EMERY — Edward S. Emery, Jr., M.D., of Brookline, died March 16. He was in his fifty-fourth year.

Dr. Emery received his degree from Harvard Medical School in 1920. He was an instructor at Harvard Medical School, as well as senior associate in medicine, Peter Bent Brigham Hospital, and medical consultant, Bedford Veterans Hospital. He was a member of the American Society for Clinical Investigation, American Gastro-Enterological Association and International Society for Gastro-Enterology and a fellow of the American Medical Association.

His father, his widow, two sons and a daughter survive.

EWING — Edward H. Ewing, M.D., of Stoughton, died March 8. He was in his seventy-fifth year.

Dr. Ewing received his degree from the College of Physicians and Surgeons, Baltimore, in 1897.

His widow survives.

HAYES — Arthur Warren Hayes, M.D., of Greenfield, died March 11. He was in his fifty-sixth year.

Dr. Hayes received his degree from Middlesex University School of Medicine in 1920. He was a member of the New England Roentgen Ray Society, the Radiological Society of North America and the American College of Radiology, and was a fellow of the American Medical Association.

A sister and six brothers survive.

HILLS — Charles E. Hills, M.D., of Natick, died February 23. He was in his seventy-eighth year.

Dr. Hills received his degree from Dartmouth Medical School in 1901. He was a fellow of the American Medical Association.

His widow, a son and three daughters survive.

RYDER — George H. Ryder, M.D., of Quincy, died March 12. He was in his seventy-third year.

Dr. Ryder received his degree from Harvard Medical School in 1899. He was a fellow of the American College of Surgeons and a member of the New England Ophthalmological Society.

His widow and a daughter survive.

MISCELLANY

NOTES

Thirty-one new faculty appointments and seven promotions at the Boston University School of Medicine were recently announced. In the Department of Medicine, John P. Rattigan was promoted to assistant professor, and James W. Culberton, Edward D. Freis, William L. Hewitt, Dera Kinsey and George W. Waring, to instructors. Burton C. Grodberg was promoted from assistant in gynecology to instructor. New appointments were as follows: Stephen Chang, assistant in medicine; Thomas L. Hartman, instructor in medicine; Timothy R. Talbot, Jr., instructor in medicine; Samuel E. Leard, instructor in medicine; William F. Caveness, instructor in medicine; Philip Kramer, assistant in medicine; Robert M. MacDonald, assistant in medicine; Louis Bachrach, assistant in medicine; William E. R. Greer, assistant in medicine; Thomas Perrin, assistant in medicine; Samuel C. Cohen, assistant in medicine; Harold L. Chandler, assistant in medicine; Donald L. John, assistant in medicine; John B. Graham, assistant in surgery; Donald Rayl, assistant in surgery; David Jennison, assistant in surgery; Robert Bolduc, assistant in surgery; Douglas Farmer, assistant in surgery; Joseph Stanton, assistant in surgery; Richard Lyon, assistant in surgery; John J. Byrne, instructor in surgery; Harry Goldman, instructor in radiology; Paul Massick, assistant in radiology; Harry Lerner, assistant in radiology; Leslie Bragg, assistant in radiology; Lazarus Secunda, instructor in psychiatry; Herbert I. Harris, instructor in psychiatry; Andrew D. Elia, instructor in gynecology; John L. Morrison, assistant in gynecology; John M. McIver, assistant in ophthalmology; and David Stearns, assistant professor of urology.

The following appointments to the teaching staff of Harvard Medical School were recently announced: Albert Burton Anderson, of Cambridge (S.B. Yale University 1932, M.D. Harvard University 1936), assistant in surgery; Henry Philip Brean, of Boston (A.B. Yale University 1937, M.D. Harvard University 1943), assistant in radiology; Johan W. H. Cammermeyer, of Oslo, Norway (M.D. University of Oslo 1940), research fellow in neurology; William Leroy Caton, of Dorchester (S.B. Springhill College 1938, M.D. Washington University 1943), research fellow in obstetrics; Albert I. C. DeFriez, of Cambridge (A.B. Princeton University 1940, M.D. Columbia University 1943), research fellow in physiology; Jane Emerson Denton, of Fort Benning, Georgia (A.B. Wellesley College 1942, M.D. Columbia University 1945), research fellow in anesthesia; Andre de Vries, of Cambridge (M.D. University of Amsterdam 1936), research fellow in medicine; Sydney Saul Gellis, of Newton Centre (A.B. Harvard University 1934, M.D. Harvard University 1938), assistant in pediatrics; Robert Spaulding Hormell of Melrose (A.B. Harvard University 1935, M.D. Harvard University 1939), assistant in surgery; Evelyn June Lorenzen, of El Reno, Oklahoma (S. B. University of Oklahoma 1942, Ph.D. Cornell University 1946), research fellow in medicine; John Kimberly Meneely, Jr., of Coeymans, New York (S.B. Yale University 1938, M.D. Yale University 1941), assistant in medicine; Dora Gerzenstein Mittelman, of Buenos Aires, Argentina (Ph.D. University of Buenos Aires 1942), research fellow in physical chemistry; Charles Galloupe Mixter, Jr., of Brookline (S.B. Trinity College 1935, M.D. Harvard University 1939), assistant in surgery; Gordon Steinbach Myers, of Needham (A.B. Harvard University 1936, M.D. Harvard University 1940), assistant in medicine; Eugene Francis Poutasse, of Worcester (S.B. Harvard University 1940, M.D. Harvard University 1943), assistant in surgery; James Alexander Taylor, of Oxford, North Carolina (A.B. University of North Carolina 1939, M.D. Harvard University 1943), assistant in medicine; Alexander Terzin, of Belgrade, Jugoslavia (M.D. University of Zagreb, Jugoslavia, 1939), research fellow in bacteriology and immunology; Suzanne Taets van Anerongen, of Amsterdam, Holland (M.D. University of Amsterdam 1942), assistant in psychiatry; and Pen-Chung Yu, of Kweiyang (Kweichow) China (M.B. National Kweiyang Medical College 1940), research fellow in bacteriology and immunology.

CORRESPONDENCE

TREATMENT OF HYPERTHYROIDISM

To the Editor: The most important problem in the field of thyroid disease today undoubtedly concerns the proper management of hyperthyroidism. Should a patient with this disease receive medical treatment followed by surgical treatment, or should he receive medical treatment alone? The problem is clear enough, and the solution is now perhaps almost as clear.

There is an unfortunate tendency to accept thyroidectomy as an entirely satisfactory method of treatment, and it is true that in the best surgical clinics the operative mortality is extremely low. But the hoarseness of recurrent laryngeal nerve paralysis, the twitch and spasm of tetany and the apathy and lethargy of myxedema are seen with sufficient frequency in patients bearing the mark of the thyroid surgeon to emphasize the fact that the surgical treatment of hyperthyroidism is something less than ideal. Moreover, there are patients who continue to exhibit the symptoms and signs of thyrotoxicosis despite one or two operations. Finally, any operation implies a certain amount of danger, discomfort, disability and financial loss. In brief, it is self-evident that any nonsurgical procedure is superior to a surgical one, provided the benefits and the risks are at least equal.

The crucial question, then, is, Have we a safe and effective nonsurgical method for treatment of hyperthyroidism? The answer, I believe, is a vigorous affirmative! In Dr. Frank H. Lahey's paper, "Surgery of the Thyroid Gland," which appeared in the January 9 issue of the *Journal*, he groups propylthiouracil with thiouracil and thiobarbital and repeatedly refers to them collectively as "dangerous drugs." This is an unfortunate and entirely misleading method of discussion. One would not consider gramicidin and penicillin together and refer to them as "dangerous." Each drug requires analysis and classification according to its own merit and its own individual toxicity, and propylthiouracil deserves critical evaluation alone, not in the company of its "dangerous" brothers. Propylthiouracil has now been used for nearly two years in several thousand patients. The mortality in the patients receiving the drug is zero. A few minor reactions have been reported, none of which required that the drug be discontinued. No clear case of agranulocytosis has yet been encountered. Undoubtedly more toxic effects will be observed in the future as the use of this chemical increases, but the rate will surely be very small. Except for penicillin, it is difficult to name an agent at once so potent and innocuous in the whole field of therapeutics!

Is the drug entirely effective? One must be more cautious in answering this question because the time elapsed since its introduction does not permit a categorical answer. But it appears quite certain that propylthiouracil is effective in reducing the metabolic rate — a controllable "medical thyroidectomy" — within a fairly short period in virtually every patient.

The evidence at hand does not allow a definite statement concerning the problem of remission and recurrence, but there is reason for optimism concerning it. Furthermore, there is no reason to suppose that recurrences, when and if they occur, cannot be retreated as safely and effectively as the original condition.

In view of the evidence now available, it seems logical to conclude that in the large majority of patients propyl-

thiouracil alone is the method of choice in the treatment of hyperthyroidism.

RALEIGH W. BAIRD, JR., M.D.
53 Greenough Street
Brookline, Massachusetts

* * *

The above letter in its original form concluded with the sentence, "It seems logical to conclude that thyroidectomy for hyperthyroidism deserves a place in the surgical graveyard, when other outmoded procedures rest in uneasy peace." This was forwarded to Dr. Frank H. Lahey, who was later informed that Dr. Baird had requested that the last sentence be changed to read as printed. Dr. Lahey's reply is as follows:

To the Editor: Dr. Baird's conclusion that subtotal thyroidectomy is outmoded in the treatment of hyperthyroidism since the advent of newer antithyroid drugs seems premature. He admits that the evidence at hand does not allow a definite statement concerning the problem of remission or recurrence on withdrawal of the drug, be it either thiouracil or propylthiouracil. The incidence of prolonged remission after the withdrawal of treatment with these drugs in patients with severe or moderately severe hyperthyroidism has, in our experience, been extremely discouraging. We agree, and have so reported, that these drugs produce remissions in patients with mild hyperthyroidism who have small goiters.

His statement that propylthiouracil can be given without danger is not substantiated by facts. There is even danger in its short-term use, as we have used it. We have observed significant blood changes in 5 of 370 patients treated with propylthiouracil. One was a typical severe case of agranulocytosis, and a fatality was prevented by energetic treatment with penicillin. The danger of development of sensitivity from repeated courses of treatment, should a relapse develop, needs further evaluation, as does the possible danger of grave histopathologic changes following prolonged maintenance treatment.

Since no hope for restoration of the thyroid gland to normal size and structure can be held by virtue of the use of these drugs, it is evident that their action cannot be curative. On the other hand, it has been our experience in a series of 750 cases that either thiouracil or propylthiouracil is entirely effective in returning the basal rate to normal in every case if given in a large enough dose over a sufficient length of time.

The possible dangers of unskillful thyroid surgery have been the basis of numerous papers from this clinic, and we are well aware of such dangers. A blanket condemnation of thyroidectomy as a useful procedure on the basis of these dangers, which can be circumvented, seems to lack logic. Similar condemnation of gall-bladder surgery because of possible injury to bile ducts may be made with this type of reasoning. There are a great many places all over the country where safe thyroid surgery is being done.

We are given the responsibility of restoring to health, in the shortest possible time, approximately 560 hyperthyroid patients each year. As our experience has shown that proper preparation of the patient with antithyroid drugs followed by thyroidectomy offers the best chance of restoration to health with minimal operative risk and morbidity and low recurrence rate, we expect on the basis of present knowledge to continue this type of treatment. This plan of treatment eliminates the uncertainty of cure that is inherent in treatment with antithyroid drugs. We shall continue to give patients with mild hyperthyroidism with small goiters or with recurrences the benefit of a trial with iodine or antithyroid drugs in the hope of inciting a remission.

FRANK H. LAHEY
605 Commonwealth Avenue
Boston 15

A COMPLICATION OF THE "FLU" EPIDEMIC

To the Editor: I have lately begun to show rather alarming symptoms. If the "flu" epidemic continues much longer, I am sure I shall become deranged. If you hear that I am standing on a street corner somewhere describing a quarter of a circle with my right arm and ending with the tip of the index finger an inch below the larynx, you will know the worst has happened. All day long I see nothing but that right arm making a quarter of a circle. For six weeks I have seen this happen. It is impossible to escape it. In every house and store, in the garage, post office and hospital and on the street the arm describes the same arc. These people say, "Doctor, right here is the trouble." They get me out of bed in the early morning to tell me about it. When I go to bed at night, if I go to bed, they are still telling me about it. They tell me not only about themselves, with the minutest detail, but also about all the other members of their families who have the bug and about all their relatives in Boston or New York or some other place who have been sick. They don't stop there; they go back a generation and tell me how they and their families suffered in 1918.

Three weeks ago a miracle occurred. The telephone hardly rang for two days. Only one or two came to the office. I said to myself: "The epidemic is over. It has been pretty tough, but a doctor has got to go through those things once in a while. Life isn't so bad after all." The sun shone brightly on those two days; the sky was a brilliant blue, and the air was like wine. "I shall relax," I said, "and work on the farm; I shall go to see my friends and gaze at the mountains beyond our valley."

I was never more deluded in my life. On the third day the telephone began to ring again, the office filled up, and the daily grind of getting in and out of a car and reaching for the little black bag was just as it had been. The arm began to describe the same quarter circle. Nothing was different except that the complaints became louder and the response to treatment wasn't so good. They told me about this in no uncertain terms and wanted to know whether I had made a mistake in the medicine and what I was going to do about it.

Two or three weeks ago I ventured out on the street. I never do that any more. I never get out of my car except when I go to the office or am making a call. It is too risky. I can't walk a quarter of a block without someone stopping me and saying: "Doctor, my husband is sick. Won't you drop around and see him?" I regard her with a dead-pan look and say, "What is the matter with him?" — all the time watching for that right arm to begin to move. "He has the flu, I guess." "What is his temperature?" "One hundred and two," "That is nothing," I say; "I should be alarmed if he didn't have a fever; some of them have a temperature of 104 or 105." (This last statement is a slight exaggeration, but there is method in it.) "But Doctor, he has an awful headache." "That is perfectly normal," I say. "They all have awful headaches. It will let up soon." "But Doctor, his cough. I am afraid it will settle on his lungs. He has weak lungs, you know. The trouble seems to be up here now." Then I see the right arm begin to move. I am licked, and after wasting ten minutes in a vain effort to get out of making a call, I go to see him.

So I have given up walking on the streets. I don't go into stores any more. If I have anything to buy, I go to the neighboring town. Sometimes it is absolutely necessary to go to the local drugstore. I slink in, keeping close to the wall, and taking advantage of any cover that presents itself until I reach the prescription desk, where I am safe. When I go out I make a plunge for the door with my head down, like a halfback going through the line.

If there was any milk of human kindness in me, there isn't any now. I am as about as sympathetic as a fish, and I look on the human race with fear and aversion. I never smile any more. I never say anything unless it is absolutely necessary. When someone asks me how I am, I say, "Fine, thank you." I wouldn't ask them how they are for any amount of money. One can't risk the consequences of a question like that.

I have gone into my symptoms and mental state in some detail, because I thought that you would want to know all the facts pertaining to my case.

NEIL C. STEVENS
Walpole, New Hampshire

RICKETTSIALPOX

To the Editor: The editorial "A New Rickettsial Infection in New York City," which appeared in the January 9 issue of the *Journal* was excellently written and quite informative.

I was particularly interested in the statement that in rickettsialpox the spleen is "palpable in about half the cases." I was aware that in some cases a palpable spleen had been reported, but I have as yet seen no data that could be made the basis for calculating the percentage of palpable spleens that occur in rickettsialpox.

The statement "Complement-fixation tests were negative for typhus fever, Rocky Mountain spotted fever, Q fever,

scrub typhus and psittacosis" is incorrect with reference to Rocky Mountain spotted fever. About 80 per cent of the convalescent serums taken fourteen days or more after the onset of rickettsialpox were positive for Rocky Mountain spotted fever in significant dilutions. In nearly all cases, however, the titer was lower when tested with the heterologous antigen than with the homologous antigen.

Possibly also worth mentioning is the misspelling of my name, both in the text and in the references. The consistent manner in which it is misspelled suggests that it is a matter of firm conviction.

ROBERT J. HUEBNER,
S. A. SURGEON

National Institute of Health
United States Public Health Service
Bethesda 14, Maryland

* * *

The information regarding the spleen and complement-fixation tests was obtained from the October, 1946, issue of the *Quarterly Bulletin* of the New York City Department of Health, but the facts as they are given in Dr. Huebner's letter are clearly stated in his papers that appeared in November, 1946, issues of *Public Health Reports*. The misspelling of Dr. Huebner's name was inexcusable, and for this, due apology is offered. — ED.

BOOK REVIEWS

Sex Problems of the Returned Veteran. By Howard Kitching, M.D. With a foreword by Ernest R. Groves. 12°, cloth, 124 pp. New York: Emerson Books, Incorporated, 1946. $1.50.

This is another book that deals with the returning veteran. It is short and is essentially a practical book. It restates much that has been said in the press and on the stage about the return of Ulysses after his Odyssey, but it presents the material compactly and in a readable manner. This book is not profound, but it abounds in common sense and emphasizes the obvious and the logical.

A reading of this volume may help to reassure persons with mild anxiety by helping them to realize that the difficulties encountered in sexual adjustments after prolonged absence from home are frequent problems with certain stock angles and well known solutions. If it serves to do even that much, its publication is well worth while. In the hands of an intelligent person, this book may do even more because of its simplicity and inclusiveness. The material is well organized.

Diseases of the Retina. By Herman Elwyn, M.D. 8°, cloth, 587 pp., with 170 illustrations. Philadelphia: Blakiston Company, 1946. $10.00.

All ophthalmologists and internists who have mastered ophthalmoscopic technic will derive much aid and considerable satisfaction from this work, which lists forty-two retinal entities catalogued in the eight sections of the book. The clinical course, complications, hereditary characteristics, pathogenesis and treatment of each entity are discussed. Of the one hundred and seventy illustrations, nineteen are in color. Each section carries its own bibliography, which facilitates reference to the authorities.

The main strength of this work, in the opinion of the reviewer, consists in the careful correlation between the clinical and the pathological aspects of each entity, and in the general clarity of the text.

The book would probably lose little and gain much if the last two sections were omitted, and the thirty-two pages thus released were devoted to the following items: an acceptable discussion of the metabolism of the retina, its dependence on the choriocapillaris, its anatomy, its physical and colloidal chemistry, as well as its photochemistry, its oxidation mechanism, the functioning of its capillaries under the pressure levels prevailing in the eye and the fragility and permeability of its capillaries — the references on Page 6 to the work of Hueck do not tell the whole story; and an attempt to interest and to inform the neurologist and the neurosurgeon, who are given one brief paragraph on papilledema on Page 54, no charts of scotomas resulting from the retinal entities and no discussion of toxins or processes that affect the retinal ganglion cells or the papillomacular bundle.

Diagnostic Examination of the Eye: Step-by-step procedure. By Conrad Berens, M.D., and Joshua Zuckerman, M.D., C.M. 8°, cloth, 711 pp., with 410 illustrations. Philadelphia: J. B. Lippincott Company, 1946. $15.00.

This clinical vade mecum, analyzing step by step the proper procedure in handling the eye patient, from the history taking down through the entire examination according to approved modern methods, should be in the hands of every young ophthalmologist when he starts the practice of the specialty. As he acquires experience and judgment, the ophthalmologist will find the short cuts to information essential to proper diagnosis and treatment. The established ophthalmologist will gain a wealth of useful, detailed information from the pages of this systematic and encyclopedic volume. The illustrations are well reproduced, and many are in color.

Music in Medicine. By Sidney Licht, M.D. 8°, cloth, 132 pp. Boston: New England Conservatory of Music, 1946. $3.00.

Physicians are cast in a unique role in modern society. They see many persons who are in need of emotional outlets in addition to treatment of whatever physical disorders they may have. The words of doctors of medicine carry so much suggestive power that it is regrettable that some fail to use this power constructively. Many facilities available for psychologic healing are neglected. Dr. Licht believes that music is particularly curative and has a unique and important place in medicine. In support of this opinion, he has gone through the existing literature on this subject and has made in addition many fresh observations of his own. He has organized the material systematically into an interesting volume that emphasizes the deeper psychologic uses as well as the more conventional, superficial advantages that music offers the receptive person. This practical and pleasant book will appeal particularly to physicians and patients who are inclined to make the most of social resources that are close at hand.

Dr. Licht writes in an informal and graceful manner. His style is provocative and spontaneous. In this book he shows appreciation of psychologic medicine as well as of music. Many people have used symphony concerts for years as a form of self-administered psychotherapy. With the radio and with music better recorded and more cheaply available than ever before, this book is especially timely.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Surgical Treatment of the Nervous System. Supervising editor: Frederic W. Bancroft, M.D., associate clinical professor of surgery, Columbia University College of Physicians and Surgeons, attending surgeon, New York City and Beth David hospitals, consulting surgeon, Veterans Administration, Lincoln and Harlem hospitals, New York City, and Kings Park State Hospital, Kings Park, New York; associate editor: Cobb Pilcher, M.D., associate professor of surgery, Vanderbilt University School of Medicine, and visiting surgeon, Vanderbilt University Hospital, Nashville, Tennessee. 4°, cloth, 534 pp., with 293 illustrations and 5 color plates. Philadelphia: J. B. Lippincott Company, 1946. $18.00.

Pneumoperitoneum Treatment. By Andrew L. Banyai, M.D., associate clinical professor of medicine, Marquette University Medical School. 8°, cloth, 376 pp., with 74 illustrations and 16 tables. St. Louis: C. V. Mosby Company, 1946. $6.50.

Neurosis and the Mental Health Services. By C. P. Blacker, M.D., F.R.C.P. With a foreword by Sir Wilson Jameson, K.C.B., M.A., M.D., LL.D., F. R. C. P., chief medical officer of the Ministry of Health and the Ministry of Education. 8°, cloth, 218 pp., with 56 tables. New York: Oxford University Press, 1946. $5.00.

Oral Medicine. By Lester W. Burket, M.D.,D.D.S., professor of oral medicine, Thomas W. Evans Museum and Dental Institute School of Dentistry, University of Pennsylvania, and professor of oral medicine, Graduate School of Medicine, University of Pennsylvania. With a section, "Oral aspects of aviation medicine," by Major Alvin Goldbush, A.U.S., D.D.S., M.S., D.S. 8°, cloth, 674 pp., with 350 illustrations. Philadelphia: J. B. Lippincott Company, 1946. $12.00.

The Modern Treatment of Diabetes Mellitus: Including practical procedures and precautionary measures. By William S. Collens, M.D., chief, Diabetic Clinic and Clinic for Peripheral Vascular Diseases, and associate visiting physician, Israel Zion Hospital, Brooklyn, associate visiting physician, Greenpoint Hospital, Brooklyn, attending metabolist, Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn, and consultant in metabolic diseases, Rockaway Beach Hospital, New York; and Louis C. Boas, M.D., assistant in Diabetic Clinic and in Clinic for Peripheral Vascular Diseases, Israel Zion Hospital, Brooklyn, chief, Diabetic Clinic, and assistant visiting physician, Greenpoint Hospital, Brooklyn, and associate in Department of Metabolism, Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn. 8°, cloth, 514 pp., with 195 illustrations. Springfield, Illinois: Charles C Thomas, 1946. $8.50.

Report on a Survey of Medical Education in Canada and the United States. By C. E. Colman, M.R.C.S. (Eng.), L.R.C.P., M.B., B.S., M.R.C.P., D.P.H., Ph.D. (Lond.), and F.A.P.H.A., professor and head, Department of Bacteriology and Preventive Medicine and Department of Nursing and Health, director, Division of Laboratories, Provincial Board of Health, and research member, Connaught Medical Research Laboratories, University of Toronto. 4°, paper, 53 pp., with 2 tables. Toronto: University of Toronto, 1946.

Motor Disorders in Nervous Diseases. By Ernst Herz, M.D., instructor in neurology, Columbia University College of Physicians and Surgeons; and Tracy J. Putnam, M.D., professor of neurology and neurologic surgery, Columbia University College of Physicians and Surgeons. 8°, cloth, 184 pp., with 250 illustrations. New York: King's Crown Press, 1946. $3.00.

Diabetes: A concise presentation. By Henry J. John, M.D. 8°, cloth, 300 pp., with 74 charts and 44 tables. St. Louis: C. V. Mosby Company, 1946. $3.25.

Narco-Analysis: A new technique in short-cut psychotherapy: a comparison with other methods and notes on the barbiturates. By J. Stephen Horsley, deputy medical superintendent, Dorset Mental Hospital. 12°, cloth, 134 pp. New York and London: Oxford University Press, 1943. $2.50.

Group Psychotherapy: Theory and practice. By J. W. Klapman, M.D., member, faculty of Northwestern University Medical School, member, Board of Psychiatry and Neurology, and staff member, Institute for Juvenile Research, Chicago. 8°, cloth, 344 pp., with 14 illustrations. New York: Grune and Stratton, 1946. $4.00.

Technique of Psychoanalytic Therapy. By Sandor Lorand, M.D., member, faculty of New York Psychoanalytic Institute. 8°, cloth, 251 pp. New York: International Universities Press, 1946. $3.50.

Nutrition and Chemical Growth in Childhood. Volume II: *Original data.* By Icie G. Macy, Ph.D., Sc.D., director, Research Laboratory, Children's Fund of Michigan, member, Food and Nutrition Board, National Research Council, and consultant for nutrition to the pediatric staff, Children's Hospital of Michigan. With a foreword by Lawrence Reynolds, M.D., editor, *American Journal of Roentgenology and Radium Therapy,* and a supplement by Julia O. Holmes, Ph.D., presenting data collected in the Department of Home Economics, Agricultural Experiment Station, College of Agriculture, University of Illinois. 8°, cloth, 1027 pp., with 705 illustrations and 474 tables. Springfield, Illinois: Charles C Thomas, 1946. $10.00.

Human Ear in Anatomical Transparencies. Descriptive text by Stephen L. Polyak, M.D., professor of anatomy, University of Chicago; anatomic transparencies and illustrations by Gladys McHugh, medical illustrator, University of Chicago Clinics; and anatomic preparations by Delbert K. Judd, M.D., assistant professor of otolaryngology, University of Chicago. 4°, cloth, 136 pp., with 83 illustrations. Elmsford, New York: Sonotone Corporation, 1946. $10.50.

Preventive Medicine and Public Health. By Wilson G. Smillie, M.D., D.P.H., Sc.D. (hon.), professor of public health and preventive medicine, Cornell University Medical College, New York. 8°, cloth, 607 pp., with 41 illustrations and frontispiece and 21 tables. New York: Macmillan Company 1946. $6.00.

NOTICES

CUTTER LECTURE

The Cutter Lecture on Preventive Medicine will be given at 5 p.m. on Tuesday, April 22, in the Amphitheater of Building D of the Harvard Medical School. Dr. Thomas M. Rivers, director of the Hospital of the Rockefeller Institute for Medical Research, New York City, will speak on the subject "Certain Public Health Aspects of Infectious Diseases."

The medical profession, medical and public-health students and others interested are cordially invited to attend.

BOSTON UNIVERSITY SCHOOL OF MEDICINE ALUMNI ASSOCIATION

The annual alumni meeting and scientific program of Boston University School of Medicine will be held on Friday, May 9.

The scientific program will be held in the auditorium of the medical school. The lectures will be open to the medical profession.

PROGRAM

10:00 a.m. The Treatment of Congestive Heart Failure. Dr. Norman H. Boyer.
10:30 a.m. The Clinical Use of Benadryl and Pyrabenzamine. Dr. Francis C. Lowell.
11:00 a.m. Newer Concepts in the Management of Asthma. Dr. John J. Curry.
11:30 a.m. The Clinical Uses of Folic Acid. Dr. Joseph F. Ross.
2:00 p.m. Recent Developments in the Treatment of Peptic Ulcer. Dr. Franz Ingelfinger.
2:30 p.m. The Use of Anesthetic Procedures in Diagnosis and Therapy. Dr. Julia Arrowood.
3:00 p.m. The Management of Acute Renal Insufficiency. Dr. Charles Burnett.
3:30 p.m. The Problem of the "Sore Throat." Dr. Louis Weinstein.

The annual meeting and banquet of the Alumni Association will be held at 7 p.m. in the Georgian Room, Hotel Statler. The guest speaker will be Francis W. Dahl, well known cartoonist of the *Boston Herald,* whose subject will be "Dahl Looks Things Over." Daniel L. Marsh, president of Boston University, will greet the alumni. Alex J. McFarland, secretary of the Class of 1930 of Dartmouth College, will speak on the subject "Dartmouth Alumni Plan." Dean Donald Anderson, of the medical school, will give a progress report. Dr. Roger M. Burgoyne, president of the Alumni Association, will preside.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING

THURSDAY, APRIL 17

FRIDAY, APRIL 18

*9:00–10:00 a.m. Studies in Histochemistry. Dr. Henry Bunting. Joseph H. Pratt Diagnostic Hospital.
*10:00 a.m.–12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

MONDAY, APRIL 21

*12:15–1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

TUESDAY, APRIL 22

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.
5:00 p.m. Cutter Lecture. Amphitheater, Building D, Harvard Medical School.

WEDNESDAY, APRIL 23

*9:00–10:00 a.m. Pediatric Clinicopathological Conference. Drs. James M. Baty and H. E. MacMahon. Joseph H. Pratt Diagnostic Hospital.
*11:00 a.m.–12:00 m. Medical Clinic. Amphitheater, Children's Hospital.

(*Notices continued on page xix*)